THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

FEBRUARY, 1934.

ORIGINAL ARTICLES.

BUNDLE-BRANCH BLOCK: A CASE ANALYSIS WITH ESPECIAL REFERENCE TO INCIDENCE AND PROGNOSIS.*

By John T. King,

ASSOCIATE IN MEDICINE, THE JOHNS HOPKINS UNIVERSITY, BALTIMORE, MD.

(From the Medical Clinic and Cardiographic Laboratory, School of Medicine, The Johns Hopkins University.)

In view of the more frequent recognition of bundle-branch block in recent years, it has become advisable to consider the various clinical implications of this condition. It is still looked upon generally as a chance finding upon the electrocardiographic tracing, interesting because of its rarity. Textbooks of medicine discuss the subject rather summarily.

This type of block is due to complete interruption of the excitatory impulse of the heart in its passage through one of the two ventricular branches of the bundle of His; while the block is doubtless due usually to an organic lesion of the heart muscle, it has been suggested by Cohn and Lewis[6] that a physiologic disturbance might produce the same effect. Reports on the pathologic anatomy of bundle-branch block are conflicting; however, nothing will be gained by reviewing this aspect of the subject here. Suffice it to say that search for the lesion causing the block has led some to state that the lesion was found on the side of the heart suggested by the electrocardiogram, others that it was found on the opposite side.

Parallel to this ambiguity of data on the pathologic anatomy of the condition is an analogous conflict of findings on the pathologic

* Presented before the Association of American Physicians at Washington, May 9, 1933.

physiology as shown by the electrocardiogram. As a result of section of the individual branches of the His bundle in the dog, Eppinger and Rothberger[8] obtained electrocardiograms that may be considered characteristic of bundle-branch block in this animal. Section of the right branch in the dog produces changes in the electrocardiogram that are similar to those found in the usual variety of block in the human being. Largely for this reason, this (usual) type of tracing, shown in Fig. 1, has been generally considered until recently to be due to block in the right bundle branch. However, Barker, Macleod, Alexander and Wilson[2] have had the opportunity to make observations on the course of ectopic contrac-

FIG. 1.

tions of the heart by stimulating directly the exposed heart in a human subject. Their results led them to believe that the common variety of bundle-branch block is due to obstruction of the excitation wave on the *left* side, not on the *right* as heretofore thought, and that the unusual type, which is characterized by a deep *S* wave in Lead I and a high *R* in Lead III, is due to right-side block. In the present communication the classification suggested by Wilson and his coworkers[2] is carried into effect and the cardiogram of the general type shown in Fig. 1 is considered as indicating *left* bundle-branch block. Otherwise, the well-known criteria for the electrocardiographic diagnosis laid down by Carter[4] formed the basis of diagnosis throughout our series.

Of reported clinical cases, Willius,[24] in 1926, collected 105, which he analyzed with especial reference to the electrocardiograms and

to prognosis. The usual (now "left side") variety of bundle-branch block occurred in 94, the unusual in 6 per cent. Auricular fibrillation was associated with the block in only 4 cases, while only 3 showed prolongation of the P–R interval to more than 0.2 second. Cardiovascular syphilis was associated with but 4 per cent, while in White and Viko's[22] series, as well as in that of Herrick and Smith,[11] it was found in 14 per cent, in Hart's[10] group in 20 per cent. Moreover, evidence of rheumatic heart disease occurred in only 2 cases of the Mayo Clinic series of 105. In the mortality table compiled from the 4 articles, Willius[24] showed that 65 per cent of the traceable patients had died of heart disease after the lapse of an average period of 12 months following the examination, while 28 per cent were living. The remainder had died of other causes.

Bach[1] found that the majority of patients with bundle-branch block in cardiovascular syphilis "did not live for more than 2 years after the first record has been obtained." In contrast to Willius'[24] series, Bach[1] reports 17 instances of syphilitic cardiovascular disease in 80 cases of branch block; 50 cases of his series fell into the category of senile heart disease, 11 into the rheumatic. One patient with the senile type was known to have lived for 14 years with the condition, another for 9. Bach[1] concludes that the prognosis is reasonably good in the senile group, bad in the syphilitic and best in the rheumatic.

It is only to be expected that groups of cardiac cases collected under a variety of circumstances and in various parts of the world will show statistical discrepancies. For example, rheumatic heart disease might be expected in a greater proportion of cases in the British Isles, and in the northern states of this country. On the other hand, the large negro population of Baltimore, which produces many cases of cardiovascular syphilis, enters largely into the records from which the figures here presented were drawn. While relatively little rheumatic arthritis occurs in this vicinity, rheumatic carditis is not rare, as shown by Longcope.[18] Presumably, the senile heart with bundle-branch block is to be found universally. One would not expect to find much variation in the incidence and prognosis of this variety, except, perhaps, in groups or localities where hard labor or poor living conditions shorten the span of life.

In our records I have been able to find 155 cases of bundle-branch block, derived from white and negro patients, from those ambulant and those confined to bed, from private and public, male and female wards. It would seem that such a group of cases derived from patients living, for the most part, in Maryland or adjacent states, should present a fair cross-section of cardiovascular disorders of all types—rheumatic, syphilitic and senile. Since the analysis of these cases differs considerably from those in the reports of Willius[24] and of Bach,[1] it seems that note should be made of it. My chief purpose, however, in making this report is to emphasize the surprising

frequency of incidence of bundle-branch block and to show the desirability of considering it an important clinical entity.

Pathologic Anatomy. Examinations to determine the exact site of the lesion causing bundle-branch block are difficult and are very rarely carried out in a completely satisfying manner. Taussig[20] has analyzed the few significant attempts of this nature. In the Hopkins series of 155 cases, autopsies were performed in 17.

The findings are summarized in Table 1:

TABLE 1.—PATHOLOGIC FINDINGS IN 17 CASES OF BUNDLE-BRANCH BLOCK.

No.	Patient.	Clinical etiology.	Pathologic diagnosis.
1.	C. W.	Arteriosclerosis	Moderate gen. A.S., marked A.S. of coronary arteries; slight myocardial fibrosis; cardiac hypert.; C.P.C. of viscera; hydrothorax.
2.	C. C.	Rheumatic fever	Deformity of thorax; patent foramen ovale; hypoplasia of aorta; mitral stenosis and insufficiency; hypert. and great dil. of heart, esp. left side; myocardial fibrosis; mural thrombi, right ventricle.
3.	P. S.	Arteriosclerosis	A.S. of aorta and coronary arteries; pulmonary emphysema; myocardial scars; cardiac hypert. and dil.; C.P.C. of viscera.
4.	E. C.	Asthma, drug addiction, exophthalmic goiter?	Exophthalmic goiter; A.S.; A.S. of aorta, with ulceration and early dissecting aneurysm; C.P.C. of viscera.
5.	S. D.	Hypertension(?)	Gen. A.S., involving esp. renal arterioles; chr. diff. nephritis; cardiac dil. and hypert.; hydrothorax; fibrous and fibrinous pericarditis and pleurisy; lobar pneumonia.
6.	G. S.	Arteriosclerosis	Chr. nephritis (arteriosclerotic); A.S.; pulmonary emphysema; cardiac dil. and hypert.; mural thrombus, right atrium; fibroma of kidney; colloid goiter; prostatic hypert.
7.	A. H.	Arteriosclerosis; hypertension; fibrous pericarditis	A.S.; chr. nephritis; marked coronary sclerosis; cardiac hypert. and dil; myocarditis; fibrous pericarditis; hypert. of islands of Langerhans; C.P.C. of viscera.
8.	G. N.	Rheumatic fever; hypertension	Syphilis; syph. aortitis involving aortic valves; mitral and aortic endocarditis, with mitral and aortic insuff.; fatty myocardium; C.P.C. of viscera.
9.	H. D.	Arteriosclerosis, with aortic stenosis and insufficiency	Aortic stenosis and insuff.; cardiac dil. and hypert.; A.S.; coronary scler.; chr. diff. nephritis; C.P.C. of viscera; hydrothorax.
10.	M. W.	Syphilis	Syph. aortitis; extreme scarring of myocardium; cardiac hypert.; mural thrombi; C.P.C. of viscera; slight scarring and round cell infilt. of kidneys.
11.	W. S.	Syphilis	Syph. aortitis with aortic insuff.; sclerosis of coronary arteries; C.P.C. of viscera; healed pulmonary tuberculosis; cholelithiasis; atrophy of cerebral cortex.
12.	J. B.	Hypertension; arteriosclerosis	A.S.; chr. fibrous myocarditis; cardiac hypert. and dil.; auricular mural thrombus; A.S. of cerebral and coronary arteries.

TABLE 1.—PATHOLOGIC FINDINGS IN 17 CASES OF BUNDLE-BRANCH BLOCK.—*Continued.*

No.	Patient.	Clinical etiology.	Pathologic diagnosis.
13.	W. B.	Hypertension; myocarditis	Chr. myocarditis; cardiac hypert.; mural thrombi, R. and L. auricles; mild A.S.
14.	J. W.	Syphilis	Syph. aortitis; aortic insuff.; myocardial scarring; cardiac hypert. and dil; mural thrombi, right auricle and left ventricle; adherent pericardium; organizing thrombi, aorta, left carotid and hypogastric arteries.
15.	J. K.	Syphilis; arteriosclerosis	Penile scar, syph. aortitis with aortic insuff.; necroses, fat accumulation and scars in myocardium; C.P.C. of viscera.
16.	E. M.	Hypertension; arteriosclerosis; syphilis	Pyelonephritis, atrophy of R. kidney; A.S. of larger arteries; cardiac hypert. and dil.; myocardial necroses with scarring; mural thrombi.
17.	H. E.	Arteriosclerosis	Gen. A.S. with calcif.; hydrothorax; C.P.C. of viscera; cardiac hypert. and dil.; aortic stenosis and insuff.; calcif. of aortic and mitral valves; emphysema; carcinoma of bladder.

A.S. = arteriosclerosis. C.P.C. = chronic passive congestion.
Hypert. = hypertrophy. Dil. = dilatation.

The gross pathologic findings may be summarized by stating that cardiac hypertrophy was noted as a diagnosis in 13 of 17 cases, dilatation in 10. Even in the 4 cases in which cardiac hypertrophy or dilatation was not specifically noted there were present one or more factors that might be expected to lead to cardiac failure—exophthalmic goiter (Case 4), syphilitic aortitis and aortic and mitral insufficiency (Case 8), syphilitic aortitis with aortic insufficiency (Cases 11 and 15). Moreover, the pathologic diagnoses lead one to deduce that cardiovascular disease was the primary, possibly the sole, cause of death in 16 cases, and that these patients died of heart failure. In Case 16, kidney disease seems to have played an important part in causing death. In connection with the possible cause of bundle-branch block it is of interest that coronary sclerosis was noted, together with fibrous changes in the myocardium in 3 cases, coronary sclerosis alone in 2 others, coronary sclerosis and myocarditis in 1; fibrous myocarditis occurred alone in 4 cases, combined with fatty degeneration in 1; fatty myocardium and chronic myocarditis each occurred once.

Diagnosis. Examination of the parallel columns showing the suspected clinical etiology and the pathologic diagnosis in each case (*vide supra*) shows a striking accuracy in the classification of cases into those of rheumatic, syphilitic and arteriosclerotic varieties during life. The presence of mitral stenosis (Case 2) argues *a posteriori* that rheumatic fever is the etiologic agent; mitral endocarditis, as in Case 8, probably falls into this category.

It is difficult to estimate, in considering Case 2, how much of the patient's disability was due to the rheumatic endocarditis, and how much the hypoplasia of the aorta, known to put a burden upon the heart, was an important factor in causing the "hypertrophy and

great dilatation of the heart, especially of the left side." One can only speculate upon the possible relation of fatigue of the left heart to the bundle-branch block, which in this case was of the unusual type (formerly considered left-side, now considered right-side block). In this case, however, the heart showed evidence of rheumatic disease, which would be a more likely causative agent in bundle-branch block, and which corresponds with the clinical impression of the etiology.

Though the clinical impressions were almost completely substantiated by autopsy in these 17 cases, the clinical evidence is sometimes conflicting and does not permit the physician to determine the etiology accurately.

Etiology. In the records of the Cardiographic Laboratory of the Johns Hopkins Hospital were found 155 instances of bundle-branch block. In 5 of these, the tracings indicated first block of one branch of the bundle, subsequently of the opposite branch only. Five cases therefore are listed with the groups of both left- and right-side block, so that only 150 individuals were concerned in the study. The etiologic agents concerned are listed in the following table:

TABLE 2.

	No. of of left B.B.B.	Per cent.	No. of right B.B.B.	Per cent.	Total No.	Total per cent.
Arteriosclerosis	95	87.2	13	12.2	108	69.5
Syphilis	12	..	2	..	14	9.0
Rheumatic fever	11	..	4	..	15	9.7
Doubtful	16	..	2	..	18	11.8
Total	134	86.4	21	13.6	155	100.0

Table 2 shows that the clinical etiology could be established with reasonable accuracy (*i. e.*, without significant conflict of data) in 137 of 155 cases of bundle-branch block, while in 18 (11.8 per cent) there was some doubt. As an illustration: a laborer, aged 44, gave a history of rheumatic arthritis and of syphilis; there was hypertension as well as evidence of arteriosclerosis, and the P–R interval of the electrocardiogram was prolonged. There was no cardiac valvular lesion to suggest either rheumatic or syphilitic cardiovascular disease, and it would seem quite impossible to make a satisfactory clinical classification of such a case.

A survey of the 15 patients in whom bundle-branch block was associated with rheumatic infection shows the distribution by age as follows:

Age.	No. of cases.	Age.	No. of cases.
24	1	44	1
32	1	45	1
34	1	46	1
38	2	50	1
39	1	51	1
40	2	57	2

Youngest, 24 years; oldest, 57 years.

Moreover, 3 patients of this group had hypertension. From the age distribution and from the fact that 3 patients already had hypertension, the rôle of degenerative cardiovascular changes must be considered in this group in addition to the primary rheumatic infection. It is interesting that branch block was not observed in any case of rheumatic carditis with age less than 24 years, and 9 of the 15 patients were 40 years of age or more, thus falling into the age group of rheumatic carditis that commonly develops secondary cardiovascular and renal complications.

It has been pointed out that the several reports of clinical studies of bundle-branch block show considerable discrepancies in the proportion of cases attributed to the various etiologic agents. Rheumatic fever was thought by Willius[24] to have caused only 2 of the 105 cases reported from the Mayo Clinic (roughly, 2 per cent). In Bach's[1] series from London, where rheumatic fever is prevalent, 11 of 80 cases (about 14 per cent) were attributed to this agent. In our series, 9.7 per cent of the entire group could be considered due to rheumatic fever with reasonable safety, as cases of doubtful etiology were classified separately.

It is not easy to determine the etiologic rôle that syphilis plays in the production of bundle-branch block. The presence of a chronic mitral stenosis argues strongly for present or past rheumatic infection; on the other hand, an aortic lesion alone may be caused by any one of the etiologic factors under consideration—certainly by rheumatic fever or syphilis, and perhaps by arteriosclerosis. The association of a positive Wassermann reaction with aortic insufficiency does not indicate that the cardiac lesion is necessarily syphilitic. Some of the differences in the proportion of bundle-branch block cases due to syphilis, as reported by various observers, may be traceable to different diagnostic criteria. In Willius'[24] series only 4 per cent of cases were thought to be syphilitic: each showed aortic insufficiency and a positive Wassermann reaction. He contrasts this finding with the 14 per cent in Herrick and Smith's[11] report and the 20 per cent in Hart's.[10] White and Viko[22] found that syphilis appeared about equally important in the production of bundle-branch block and complete *A–V* block (8 to 10 per cent). Our series is very similar to that of White and Viko,[22] in showing 9 per cent of cases due to syphilis. Of the 14 instances of bundle-branch block in our series attributed to syphilis, analysis shows that 5 came to autopsy and that each showed a characteristic syphilitic aortitis. It has been pointed out that the negro influence upon the hospital population in the present series should afford a particularly good opportunity to study the relation of syphilis of the cardiovascular system to bundle-branch block. Carter and Baker[5] have shown that 10.51 per cent of all patients admitted to the medical service of the Johns Hopkins Hospital show a positive Wassermann reaction in the blood; in the white race the incidence is 6.90 per cent, in the negro, 25.72. This 10.51

per cent constituted 2196 patients over a period of 12 years. Of this total number of syphilitic individuals, 488 (22.22 per cent) had evidence of syphilitic disease of the aorta; the proportion was only 13.93 per cent, however, among white patients as against 32.61 per cent among negroes. Such figures show, of course, that the negro race is much more liable to cardiovascular syphilis than is the white, at least insofar as can be determined from patients admitted to hospital. Therefore, if syphilis is an important cause of bundle-branch block, more cases of this condition should be found in groups that include negroes than in those derived from whites alone. Such, however, is not the case; for example, Bach[1] reported an incidence of 17 cases of bundle-branch block due to syphilis in a series of 80 (21 per cent). In Carter and Baker's[5] report it is shown that 488 cases of cardiovascular syphilis were encountered in the medical service of the Johns Hopkins Hospital in a 12-year period (January 1, 1918 to February 20, 1930). During a slightly shorter period (January 1, 1918 to January 1, 1930) only 119 cases of bundle-block due to all causes were found. As shown above, syphilis may be considered the cause of bundle-branch block in 9 per cent of our cases; hence those due to syphilis for the 12 years would be represented as 119 × 9 (per cent) = 10.89. In other words, the 488 cases of cardiovascular syphilis contained only 10.89 cases of bundle-branch block, or approximately 2 per cent.

Age. The average age has been computed for the three major groups, which have been separated according to etiology: the cases of doubtful etiology are not included.

TABLE 3.—AVERAGE AGE OF PATIENTS WITH BUNDLE-BRANCH BLOCK.

	Right B.B.B.		Left B.B.B.		Total average.	
	Yrs.	Mos.	Yrs.	Mos.	Yrs.	Mos.
Arteriosclerotic . .	61	2	61	5	61	4.3
Syphilitic	31	0	44	2	42	3.3
Rheumatic	46	1	40	10	42	4.0

As there were only 19 instances of right-side block included in Table 2, the average ages for the three groups in the first column cannot be considered very significant. However, the figures for the left-side groups and the total averages doubtless represent a fairly reliable age figure to be expected in each category.

Previous Infections. The histories of the 150 patients in this study were examined for significant previous infections. The results were as follows:

TABLE 4.—INCIDENCE OF PREVIOUS INFECTIONS OTHER THAN SYPHILIS AND RHEUMATIC FEVER.

Left B.B.B.	Typhoid.	Malaria.	Pulm. tbc.	Diphtheria.	Smallpox.	Pneumonia.	Tonsillitis and quinsy.
Arteriosclerotic group	20	15	1	9	2	18	7
Syphilitic group . .	0	1	0	1	1	2	1
Rheumatic group .	2	1	0	1	0	2	5
Right B.B.B.							
Arteriosclerotic group	4	1	0	3	1	3	3
Syphilitic group . .	0	0	0	1	0	0	0
Rheumatic group .	1	1	0	0	0	0	2

It must be remembered, of course, that block of the left branch is much more common than that of the right, and that the cases of arteriosclerotic etiology form the bulk of all cases. When these facts are taken into consideration the analysis of previous infections seems to show no relation of significance between the usual major infections and bundle-branch block, with the exception of tonsillitis and quinsy; the higher relative incidence of these disorders in the rheumatic group is to be expected.

TABLE 5.—OCCUPATION OF PATIENTS WITH BUNDLE-BRANCH BLOCK.

Left B.B.B.	Laborer.	Housewife.	Business.	Profession
Arteriosclerotic group	41	22	14	6
Syphilitic group	7	3	1	1
Rheumatic group	7	1	3	0
Right B.B.B.				
Arteriosclerotic group	7	2	1	0
Syphilitic group	1	1	0	0
Rheumatic group	3	0	1	0

Occupation. The occupations of the entire group are not listed, some being unknown. In view of the fact that most of the cases were drawn from patients in the public wards and dispensary, it is not surprising that the largest total incidence of the condition occurred among laborers. It seems clear, however, that the more sheltered occupations—housewife, business and professions—do not offer complete immunity to the condition. In the total population at Johns Hopkins Hospital the occupations of 500 patients were found to be as follows:

TABLE 6.—OCCUPATIONS.

Public and Private Wards (Medical), January, 1928.	
Laborer	80
Housewife	95
Business	62
Profession	63
Total (male, 171; female, 129)	300
Dispensary (Medical), January, 1928.	
Laborer	110
Housewife	63
Business	19
Profession	8
Total (male, 120; female, 80)	200

The above figures represent the first 300 and 200 occupations of house patients and dispensary patients (medical), respectively, for January, 1928.

Comparison of the occupations of patients with bundle-branch block with those of the entire hospital and dispensary medical patients shows, in percentage:

	B.B.B., per cent.	Entire hosp. population, per cent.
Laborer	54.1	38.0
Housewife	23.8	31.6
Business	16.4	16.2
Profession	5.7	14.2
Total	100.0	100.0

Thus it appears that laborers, as a class, are more prone to develop bundle-branch block than are the other classes, and that housewives show less tendency to this than to other types of disease, as do those who follow the professions.

When a further comparison is made of these two groups with patients showing heart disease other than bundle-branch block, the results are as follows:

	B.B.B., per cent.	Entire hosp. population, per cent.	Heart cases except B.B.B., per cent.
Laborer	54.1	38.0	47.6
Housewife	23.8	31.6	30.4
Business	16.4	16.2	14.2
Profession	5.7	14.2	7.8
Total	100.0	100.0	100.0

Thus it would seem that the occupation of laborer predisposes to heart disease in general as well as to bundle-branch block. (In each control group the data were drawn from 300 public ward and private house patients and 200 dispensary patients.)

Sex. Of 150 patients, 109 (73 per cent) were males, 41 (27 per cent) females. This makes it appear that the condition is more common in men. As shown above, bundle-branch block affects all classes of men; it is possible that the greater physical activity of men in all walks of life makes them more liable to this condition, as suggested by the greater incidence of angina in men. It is an interesting coincidence that White[21] has reported the occurrence of angina pectoris in 100 consecutive private patients as 73 in men, 27 in women. Moreover, there may be a similarity in the pathology of bundle-branch block and angina: this is suggested by the fact that White and Viko,[22] in a study of various forms of heart-block, observed that the anginal syndrome occurred four times as frequently in patients with bundle-branch block as in those with complete *A–V* dissociation.

Incidence. It is not easy to determine the incidence of bundle-branch block in the entire population. The chief difficulty lies in the fact that the diagnosis is usually made by electrocardiography, and was not made in any other way prior to 1928, when I[15] suggested that the diagnosis is possible from physical signs. For statistical purposes, however, it is wise to consider only cases verified by electrocardiogram. The other handicap to the statistical analysis is that electrocardiography, prior to the last several years, was used chiefly in the elucidation of the arrhythmias. There is little doubt that cases of bundle-branch block were largely unrecognized 15 and even 10 years ago. Indeed, it is my opinion that the condition is still overlooked not infrequently, even in our best clinics. In 1923 White and Viko[22] were able to collect and report 27 cases of complete heart block (a condition that is usually recognized) as compared with 41 cases of bundle-branch block. It will be shown

that bundle-branch block is now found much more often than auriculoventricular block, at least in Baltimore.

Beginning with 1 case in 1917, the records at Johns Hopkins show 23 cases recognized in 1930. Chart I shows that the number of cases that were found increased gradually until 1924; thereafter there has probably been no significant change in the diagnosis rate. In an effort to explain the marked increase of bundle-branch block the possible effect of the age of the hospital population was investigated. Inasmuch as the most important etiologic agents in its

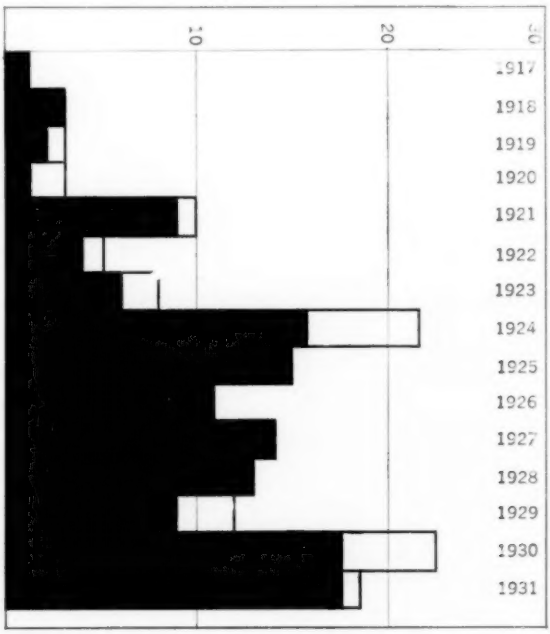


CHART I.—Cases of bundle-branch block at Johns Hopkins Hospital. The solid blocks represent left side block; the open blocks, right side block.

production seem to be age and arteriosclerosis, any significant increase in the average age of the hospital population might cause a greater incidence of bundle-branch block.

To throw light on this point the average age of the hospital patients admitted to the medical service was determined from 550 admissions in 1920 and in 1930. The results are shown in Chart II. The average age of 350 patients admitted consecutively in January and February, 1920, was 35.3 years; while an equal number in January, February and March, 1930, showed an average age of 42.6 years. It was noted, however, that influenza was prevalent among student nurses, medical students and staff physicians in 1920; as

the age of such patients would be expected to reduce the average, the average age during the summer months of July and August was determined: 200 consecutive patients in 1920 had an average age of 41.8 years, a similar number in 1930 an average age of 40.3 years. It cannot be said, therefore, that there is evidence of any significant increase in the average age of the population of the medical service at the beginning and end of the last decade.

Looking at the last two columns of Chart II, one sees that the average span of life of the entire community in Maryland has increased materially between 1920 and 1930. The Bureau of Vital Statistics of the Department of Health of the State of Maryland has found that the average life span in 1920 was 41.2 years, while in 1930 it was 49.2 years—surely an important change. Why is

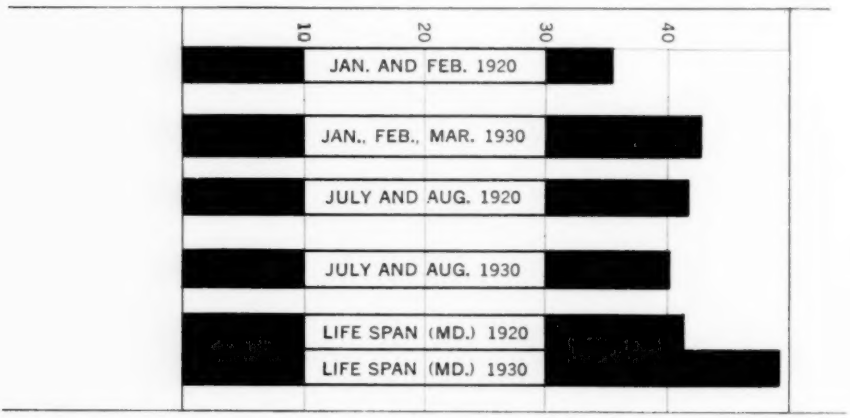


CHART II.—*Columns 1 to 4.* Comparison of the average age of the hospital population in the winter and summer of 1920 and 1930. (J. H. H. Medical service.) *Columns 5 and 6.* Comparison of the average duration of life in Maryland in 1920 and 1930.

this fact not reflected in the average age of the patients in this series? The answer doubtless lies in the fact that only patients over 12 years of age are admitted to the medical service. Since the greatest factor in the prolongation of the *average* life has been the reduction of infant mortality, such an improvement is not reflected in a group of individuals all of whom have already reached the age of 12 years.

It is obvious that conditions that permit more individuals to reach maturity will cause an increase in the relative number of individuals in the community who will be liable to adult diseases of all kinds. Thus, if individuals with ages between 50 and 70 years constituted only, say, 10 per cent of the population in 1920, and those of similar ages constituted 20 per cent in 1930, the liability of the community to bundle-branch block would doubtless be much

increased. On the other hand, there is no apparent reason why the incidence of this condition should increase per unit of population; in other words, 100 individuals admitted to the adult wards in 1930 should show no more cases of bundle-branch block than a similar number in 1920.

The question of the cause of the increasing incidence of this condition in our records was prosecuted further by comparing the number of cases from 1917 to 1931 inclusive with the incidence of heart disease of all kinds in Maryland. Chart III shows this comparison. It is clear that deaths from heart disease have increased steadily since 1906, regardless of color: the trend in the two races is similar. The death rate for 100,000 population has more than doubled for the white race between 1906 and 1930; among the

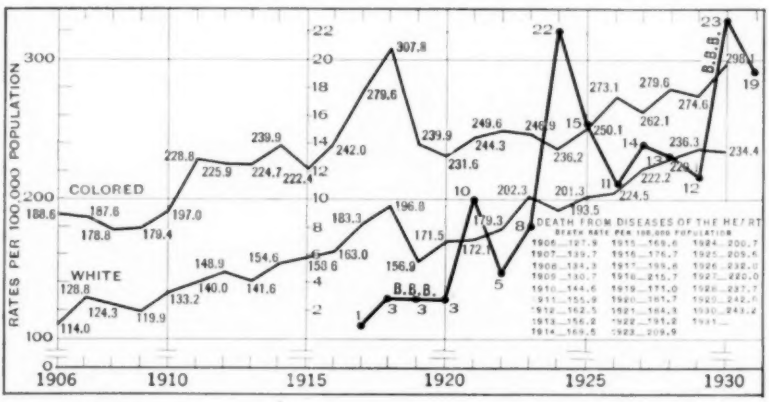


CHART III.—Deaths from diseases of the heart.—Rates per 100,000 population, white and colored. Int. List Nos. 87–90. State of Maryland, Department of Health, Bureau of Vital Statistics. Compare with incidence of B.B.B.

negroes the rate has risen from 188.6 to 298.1 (37 per cent). On a different scale, the incidence of bundle-branch block is plotted, from 1917 to 1931.

It can be seen at a glance that the increase in the number of cases of bundle-branch block diagnosed between the years indicated is much more sharp than the increase in the total deaths from heart disease. Such a rise in the diagnosis of this condition cannot be due to the increase in total heart disease rate, nor is it due, as shown above, to increase in age of the hospital population. The only possible conclusion is that the diagnosis is being made with greater regularity than formerly, due to the increasing use of the galvanometer. Moreover, the rise in recognized cases occurred before any attempt was made to diagnose or to suspect bundle-branch

block from physical signs; it is clear, therefore, that the cases were found accidentally from electrocardiographic tracings made for the purpose of throwing light on the condition of the heart muscle and of the conduction apparatus.

Comparisons have been made to show the relation of bundle-branch block to other major diseases and to other disturbances in the mechanism of the heart beat in point of frequency. The records of the year 1930 were taken for this purpose, not because the peak of incidence of bundle-branch block occurred in that year, but because it was the last year for which all records were available. Chart IV shows that bundle-branch block was found in more

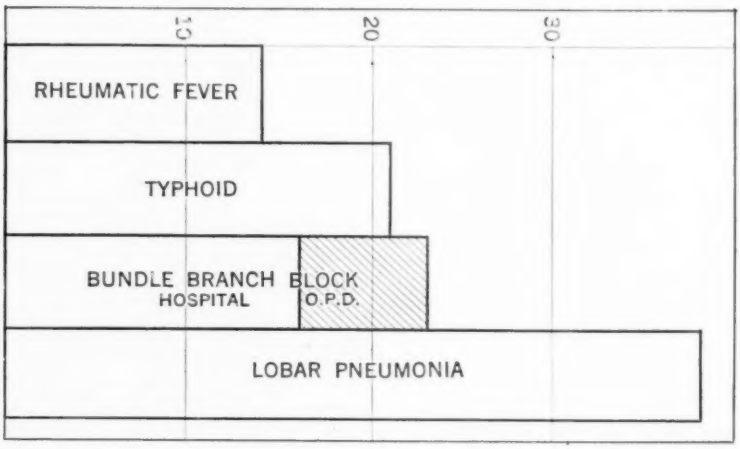


CHART IV.—Comparison of the incidence of four conditions at Johns Hopkins Hospital in 1930.

cases than was rheumatic fever or typhoid fever; while the Out-patient Department cases are included, it is probable that the 7 instances included from that source would be more or less equalled by the inevitable cases that pass through hospital wards unrecognized. In making this comparison, it should be said that the 14 cases of rheumatic fever shown in this table were instances in which this diagnosis was added formally to the hospital record; evidence of previous rheumatic infection, such as mitral stenosis, was disregarded.

Longcope[18] has recorded the incidence of rheumatic fever in all its manifestations—rheumatic arthritis, carditis, chorea, mitral stenosis, and so on, at Johns Hopkins Hospital. Over a 5-year period (September 1, 1925, to October 1, 1930) 142 cases of this nature were admitted to the medical service—an average of 28.4 cases annually. Since the year 1924 (the first year during which bundle-branch block seems to have been found in a representative

number of cases), bundle-branch block from all causes has occurred in an average number of 16 per year. It has been shown that 9.7 per cent of our cases of this type of block are of rheumatic origin; thus it follows that a proportion of 1.55 cases (16×0.097) of bundle-branch block of rheumatic origin are admitted annually. The total admissions for rheumatic infection being 28.4 per year it follows that bundle-branch block from this cause is comparatively rare—$\left(\frac{1.55}{28.4}\right) = 5.5$ per cent. As this figure (5.5 per cent) is computed upon *all* types of rheumatic infection, and not necessarily rheumatic carditis (though most patients in Longcope's[18] series had some evidence of carditis) it appears that rheumatic fever is more likely to produce bundle-branch block than syphilis, when it is remembered that such block was found in only 2 per cent of cases of syphilis known to have attacked the cardiovascular system.

In Chart V is shown the relative incidence of various disorders

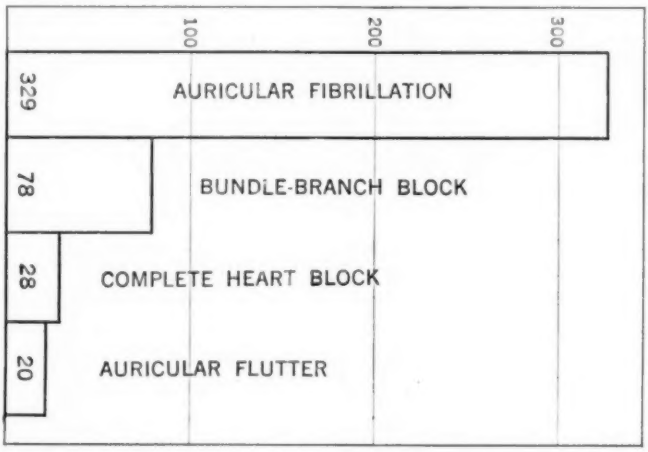


CHART V.—Incidence of disorders of the mechanism of the heart at Johns Hopkins Hospital for 5 years (January 1, 1927, to December 31, 1931).

of the mechanism of the heart beat for 5 years (1927 to 1931 inclusive) in the Johns Hopkins Hospital. Extrasystolic arrhythmia, sinus arrhythmia and the atypical or partial forms of heart-block of all types have not been considered. It will be seen that bundle-branch block was recognized in 78 cases as against 329 cases of auricular fibrillation, or somewhat less than one-fourth as commonly. On the other hand it was found in almost 3 times as many cases as complete auriculoventricular block (78:28) and just less than 4 times as commonly as auricular flutter (78:20). It is obvious that no accurate estimate can be made of the number of cases of bundle-branch block that go unrecognized; on the other hand,

auricular fibrillation and complete heart block meet a correct diagnosis in every case, to all intents and purposes.

Diagnosis. At the present time the diagnosis of bundle-branch block for statistical purposes must rest upon the electrocardiogram. Only cases that fulfilled Carter's[4] criteria are considered in this series. However, King[15] and, later, King and McEachern[16] have shown that the diagnosis (verified by electrocardiogram) can be made from physical signs alone in a proportion of cases that compares favorably with the results of attempts at the diagnosis of any other cardiac disorder. The most important physical sign is a reduplication of the apex thrust—a quick repetition of the apex impulse; this may be seen in 84 per cent and felt in 80 per cent of all cases. In addition a survey of the auscultatory findings of a considerable number of cases reveals some important modifications. In reviewing the literature one finds that the auscultatory phenomena have been recorded with some degree of faithfulness, while the more important visible and palpable reduplication has been almost consistently ignored or overlooked. For example, Mackenzie[19] and Carter[4] noted reduplication of the first heart sound, Eppinger and Rothberger[8] and Eppinger and Stoerk[9] "gallop rhythm," while Kauf[14] reported division of the apical systolic murmur. In more recent clinical studies, Hill[12] says that the heart sounds in all cases of his series were faint and in 1 case inaudible; he also found reduplication of the first heart sound, with and without a systolic murmur. Herrick and Smith[11] found "muffling" of the first sound and gallop rhythm common, while Willius,[24] report was similar, the sounds being described as lacking in definition and differentiation.

Our experience is quite in accord with these various auscultatory phenomena. In Chart VI I have attempted to delineate the different variations of the heart sounds and murmurs as I have heard them in cases of bundle-branch block. The schema is from Howell,[13] after Einthoven and Geluk. No attempt at accurate timing of the various elements was made, as the diagram is intended to convey merely impressions of audition. It will be noted that the first sound is represented throughout as faint except in the first line, where the sounds are shown as normal; this muffling, or reduction in intensity, amounting in some cases virtually to inaudibility of the first sound, is one of the most common and striking signs. However, even when the sound is inaudible one obtains, perhaps through the lift of the stethoscope, a sense of reduplication at the beginning of systole: I have attempted to represent such a finding on the 4th line. The shaded blocks which take the place of the second element of the first sound (as in Line 5) and of both elements of the first sound (as in Line 6) represent murmurs in systole. I have not attempted to list these auscultatory findings in point of frequency, since the clinical examinations were made by so many different observers as to make such a record of little value.

It cannot be emphasized too strongly that the auscultatory findings are of secondary importance to the visible and palpable reduplication of the systolic thrust in the bedside diagnosis of bundle-branch block. Where there is an apparent contradiction between the surface findings at the cardiac apex and the auscultatory signs, the auscultatory signs should be disregarded. As secondary, supporting indications, however, they are of some interest.

In a previous communication[15] I assumed that the reduplication of the first sound and the bifid apex thrust in bundle-branch block are associated with asynchronous movements of the ventricles. Previous experimental evidence had indicated that asynchronism of the ventricles follows section of one of the bundle branches.

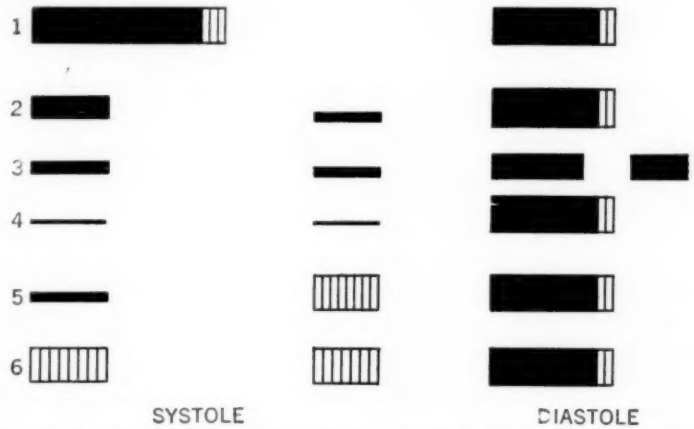


CHART VI.—A diagrammatic suggestion of auscultatory phenomena of bundle-branch block. 1, Normal sounds—an occasional finding; 2, reduplication of S_1 (common); 3, reduplication of S_1 and S_2; 4, almost complete absence of S_1; 5, soft S_1 with an asynchronous murmur; 6, asynchronous systolic murmurs.

This view is substantially strengthened by the recent work of Wolferth and his colleagues,[25] who have produced evidence of asynchronism of the ventricles in bundle-branch block in the human being, and have also shown that the reduplication of the first sound appears during ventricular systole.

Associated Electrocardiographic Findings. Bundle-branch block may coëxist with various degrees of auriculoventricular delay or block. In our series the auriculoventricular conduction time was more than 0.2 second in 24 cases of left branch block; of these, 19 instances were found in arteriosclerotic hearts, 3 in syphilitic, 2 in rheumatic. Right-side block was associated with delay in the P–R interval in 4 cases, 3 with arteriosclerotic heart disease and 1 with rheumatic. Thus, there seems to be no definite tendency for auriculoventricular delay to result from lesions of any particular etiology, as the distribution of those cases in the etiologic groups is

not dissimilar to that of the entire group. Of the entire group of 155 instances of branch block, prolongation of the *P–R* interval occurred in 28 (18 per cent).

Complete auriculoventricular dissociation coëxisted with bundle-branch block in a striking number: 27 such instances occurred with left-side block, 20 in arteriosclerotic hearts, 5 in syphilitic, 2 in rheumatic; of 9 instances found associated with right-side block, 6 occurred in arteriosclerotic, 2 in syphilitic, 1 in rheumatic heart disease. Here again there is no suggestion that any one etiology is concerned especially in the production of the *A–V* block. When complete heart block occurs with branch block there is a definite tendency for the ventricular block to shift from side to side; of a total number of 36 instances in which the two types of block coexisted, the ventricular block shifted from one side to the other in 5. In 1 case it was thought that the origin of the impulse was not in the main stem below the site of *A–V* block, but probably first in one ventricle and subsequently in the other.

Taking both degrees of *A–V* block together it is found that such block coëxisted with a branch block 64 times (41 per cent). Such a large number of cases suggests either that lesions of the main stem are commonly associated with those of a branch, or that a common lesion of the main stem at or near the bifurcation may cause both auriculoventricular and bundle-branch block in the same heart. Until more data on the pathology of these lesions is available, it is useless to pursue speculation further.

Auricular fibrillation was found in 22 of our cases of left-side block; in 19 the etiology was arteriosclerosis, in 3 rheumatic infection; of the right-side cases, fibrillation was found in 2 arteriosclerotic and 2 rheumatic hearts. No case of syphilitic etiology was found, which is in accord with the observations of others on syphilitic heart disease in general. Thus fibrillation occurred in a total of 26 cases (16 per cent). This is in contrast with the figures of Willius,[24] who found fibrillation in only 4 of 105 cases of bundle-branch block.

Auricular flutter was found in 3 cases; in each the block was of arteriosclerotic etiology and in the left bundle branch.

Prognosis. It has been pointed out that the prognosis, as indicated in previous reports, is of extreme gravity in bundle-branch block in general. However, Bach[1] found the expectancy of life is good in the rheumatic group, reasonably good in the senile, bad in the syphilitic. The unanswered question has always been: how much is the prognosis influenced by the block *per se* and how much by the condition of the heart as a whole? This cannot yet be answered.

It has been possible to trace 104 cases in our series; in each category the average duration of life after the first electrocardiographic diagnosis is indicated.

Patients Reported Dead.

	Right branch.		Left branch.		Total.	
Etiology.	No.	Life duration.	No.	Life duration.	No.	Average life.
Arteriosclerosis	7	6 mos.	47	1 yr. 1 mo.	54	1 yr.
Syphilis	2	1 yr. 0.5 mo.	10	10.3 mos.	12	10.6 mos.
Rheumatic fever	4	2 yrs. 11 mos.	6	11.5 mos.	10	1 yr. 8 mos.
	13		63		76	

Patients Reported Living.

	Right branch.		Left branch.		Total.	
Etiology.	No.	Life duration.	No.	Life duration.	No.	Average life.
Arteriosclerosis	3	8.3 mos.	20	1 yr. 11 mos.	23	1 yr. 9 mos.
Syphilis	0	0	1	1.5 mos.	1	1.5 mos.
Rheumatic fever	0	0	4	2 yrs. 8 mos.	4	2 yrs. 8 mos.
	3		25		28	

Little interpretation of these figures is necessary. Owing to the paucity of cases of right-side block, no definite conclusions can be reached as regards prognosis in block of one branch as compared with that of the opposite branch. Our figures are in accord with those of Bach[1] in that the average length of life of patients who were reported dead as well as of those reported alive was greatest in cases of rheumatic etiology. It must be remembered, however, that the average age of the rheumatic patients was considerably less than that of the senile group, hence the general vitality of the subjects should be considered in connection with the prognosis. In all patients with senile or syphilitic heart disease who were reported dead, the average duration of life following the diagnosis was a year or less. The average length of life of those reported alive was 1 year, 9 months in the senile group and 1.5 months in 1 syphilitic case.

Thus it is clear that the prognosis in bundle-branch block in general is exceedingly grave, as derived from our experience. We have seen no such protracted cases as those reported by Bach,[1] one of whose patients with bundle-branch block in senile heart disease was followed for 14 years and another of similar etiology for 9 years, and by Bishop and Bishop,[3] who report an instance of 11 years' duration. The longest period over which a patient in our series with senile heart disease and bundle-branch block has been observed is 6 years and 6 months; among those with syphilitic heart disease the longest duration was 2 years and 1½ months; in the rheumatic group the case of greatest observed duration was 6 years and 7 months.

It should be recalled, however, that the apparent expectancy of life for any group of patients with cardiac disease might be expected to be less among those who seek hospital care than among similar patients in general, since the fact of their being in hospital indicates that the disorder has already produced symptoms of greater or less severity.

Is the bundle-branch block itself concerned in the gravity of prognosis or does the course of the disorder depend upon the condition of the heart in other respects? It is very difficult to arrive at any conclusion of this question in the very heterogeneous group of senile cardiopathies, while the uncertainty as to the time of onset of heart disease in many rheumatic cases makes a determination of the duration very difficult. However, it is possible to compare syphilitic heart disease with bundle-branch block with a similar group without block. It has been possible to obtain subsequent reports of 13 patients with bundle-branch block in syphilitic heart disease; as shown in the following table, 12 were reported dead, only 1 living.

TIME INTERVALS—SYPHILITIC CASES OF BUNDLE-BRANCH BLOCK REPORTED DEAD—AVERAGE.

	Left B.B.B.	Right B.B.B. (2 cases).	Total average, R. and L. B.B.B.
From onset of symptoms to ekg. diagnosis	2 yrs. 2.8 mos. (11 cases)	1 yr. 1.5 mos.	2 yrs. 0.7 mo. (13 cases)
From ekg. diagnosis to time of report	10.3 mos. (10 cases)	1 yr. 0.5 mo.	10.6 mos. (12 cases)
Total interval from symptoms' onset to final report	3 yrs. 3 mos. (10 cases)	2 yrs. 2 mos.	3 yrs. 0.7 mo. (12 cases)

TIME INTERVALS—SYPHILITIC CASES OF BUNDLE-BRANCH BLOCK REPORTED LIVING—AVERAGE.

	Left B.B.B. (1 case).	Right B.B.B. (0 case).	Total average, R. and L. B.B.B. (1 case).
From onset of symptoms to ekg. diagnosis	3 yrs.	0	3 yrs.
From ekg. diagnosis to time of report	1.5 mos.	0	1.5 mos.
Total interval from symptoms' onset to final report	3 yrs. 1.5 mos.	0	3 yrs. 1.5 mos.

Treatment of these cases was not standardized: 1 patient only received adequate treatment for a year or more, the others being treated lightly or not at all. Carter and Baker,[5] quoting Danglade, have shown that patients with syphilitic heart disease and aortic insufficiency may be expected to live for an average time of 22 months from the onset of symptoms if little or no treatment is given, while carefully treated patients live 35 months (average). Our patients with bundle-branch block and syphilitic heart disease who were reported dead lived an average time of 36.7 months. In our series, therefore, patients who were, for the most part, treated little or not at all, lived an average time that exceeded that of the well-treated patients in Danglade's series. It is obvious that the intercurrence of bundle-branch block did not cause the patients of our series to die sooner than would be expected in any group of individuals with syphilitic heart disease.

Summary. 1. An analysis of 155 instances of bundle-branch block in 150 patients is reported.

2. In 17 cases in which autopsies were obtained a close correlation between clinical and pathologic diagnoses was found. No attempt was made to determine the exact site of the lesion.

3. Arteriosclerotic heart disease was the background in 69.5 per cent of cases, syphilis in 9 per cent, rheumatic infection in 9.7; in 11.8 per cent the etiologic agent was in doubt.

4. Comparison shows that bundle-branch block may be expected to occur in only about 2 per cent of all patients suffering from syphilitic cardiovascular disease and in 5.5 per cent of all patients with rheumatic infection of various types, at least in the vicinity of Baltimore.

5. The average age of patients showing bundle-branch block associated with senile heart disease is 61 years, 4.3 months; of those with syphilitic heart disease 42 years, 3.3 months; of those with rheumatic heart disease 42 years, 4 months.

6. Previous infections appeared to play no specific part in the etiology of bundle-branch block except in the rheumatic group, in which the history of tonsillitis and quinsy was relatively high.

7. While no social class is immune to branch block, it occurs most frequently among laborers, least frequently among housewives and those following professions: business men show an incidence to the condition in proportion to their number in the whole hospital population.

8. Men constitute 73 per cent, women 27 per cent of patients in the series; exactly similar proportions have been reported by White[21] in angina pectoris.

9. The number of cases of bundle-branch block found at Johns Hopkins Hospital increased sharply from the year 1917 to 1924, with no significant change thereafter.

10. In the year 1930 bundle-branch block was found more frequently in the medical wards of the Johns Hopkins Hospital than rheumatic or typhoid fever, though less frequently than lobar pneumonia.

11. Over a 5-year period, 329 instances of auricular fibrillation were met with; during the same period were found 78 cases of bundle-branch block, 28 of complete auriculoventricular dissociation, and 20 of auricular flutter.

12. Various auscultatory phenomena encountered in bundle-branch block are recorded in diagrammatic form. It is emphasized that such signs are of less aid in establishing a diagnosis based on physical signs than are the surface movements of the cardiac apex.

13. Prolongation of the *P–R* interval occurred in 28 cases of branch block (18 per cent); complete *A–V* dissociation occurred in 36, auricular fibrillation in 26, flutter in 3.

14. Of 104 patients who could be traced, 76 were reported dead; the average duration of life following the diagnosis of bundle-branch block was 1 year for the senile group, 10.6 months for the syphilitic and 1 year, 8 months for the rheumatic group.

Of 28 patients reported to be alive, the average time between diagnosis and the report was 1 year, 9 months in the senile group, 1.5 months in the syphilitic, 2 years and 8 months in the rheumatic.

Conclusions. 1. Most instances of bundle-branch block occur in association with degenerative (senile) heart disease, though a smaller number are found with about equal frequency in syphilitic or rheumatic infections of the heart.

2. The proportion of cases is somewhat higher in rheumatic heart disease, in general, than in syphilitic.

3. Laborers are more prone to develop bundle-branch block than are professional men or housewives, while business men are neither predisposed nor immune. The condition is more common among men than women.

4. In order of incidence, the important pathologic disorders of cardiac mechanism may be listed as follows: auricular fibrillation, bundle-branch block, auriculoventricular heart block, auricular flutter.

5. First degree heart block and complete A–V dissociation are found commonly associated with bundle-branch block.

6. The prognosis is very grave, regardless of etiology, though it appears best in those cases of rheumatic etiology. The occurrence of bundle-branch block seems to add nothing to the gravity of the prognosis of syphilitic heart disease. Since some individuals live for a considerable period with bundle-branch block, perhaps its presence should be looked upon as an omen of very grave import rather than as a necessarily fatal handicap.

7. Bundle-branch block should be considered one of the rather common, as well as important, clinical entities.

REFERENCES.

1. Bach, F.: Quart. J. Med., 1930, **23**, 261.
2. Barker, P. S., Macleod, A. G., Alexander, J., and Wilson, F. N.: Trans. Assn. Am. Phys., 1929, **44**, 125.
3. Bishop, L. F., and Bishop, L. F., Jr.: J. Am. Med. Assn., 1932, **98**, 398.
4. Carter, E. P.: Arch. Int. Med., 1914, **13**, 803.
5. Carter, E. P., and Baker, B. M., Jr.: Johns Hopkins Hosp. Bull., 1931, **48**, 351.
6. Cohn, A. E., and Lewis, T.: Proc. New York Path. Soc., 1914, **14**, 208.
7. Cowan, J., and Bramwell, J. C.: Quart. J. Med., 1925, **19**, 95.
8. Eppinger, H., and Rothberger, J.: Ztschr. f. klin. Med., 1910, **70**, 1.
9. Eppinger, H., and Stoerk, O.: Ibid., 1910, **71**, 157.
10. Hart, T. S.: Arch. Int. Med., 1925, **35**, 115.
11. Herrick, J. B., and Smith, F. M.: Am. J. Med. Sci., 1922, **164**, 469.
12. Hill, I. G. W.: Quart. J. Med., 1930, **33**, 15.
13. Howell, W. H.: Text-book of Physiology, Philadelphia and London, W. B. Saunders Company, 1930, p. 562.
14. Kauf, E.: Ztschr. f. klin. Med., 1924, **98**, 126.
15. King, J. T.: Am. Heart J., 1928, **3**, 505.

16. King, J. T., and McEachern, D.: Am. J. Med. Sci., 1932, **183**, 445.
17. Leimbach, R. F., and White, P. D.: Am. Heart J., 1927, **3**, 442.
18. Longcope, W. T.: Ann. Int. Med., 1931, **5**, 401.
19. Mackenzie, J.: Diseases of the Heart, London, Oxford Univ. Press, 1918.
20. Taussig, H. B.: Johns Hopkins Hosp. Bull., 1929, **47**, 40.
21. White, P. D.: Nelson Medicine, New York, Thos. Nelson & Sons, 1923, **4**, 621.
22. White, P. D., and Viko, L. E.: Am. J. Med. Sci., 1923, **165**, 659.
23. Willius, F. A.: Clinical Electrocardiography, Philadelphia and London, W. B. Saunders Company, 1922.
24. Willius, F. A.: Am. Heart J., 1926, **1**, 576.
25. Wolferth, C. C., Margolies, A., and Bellet, S.: Tr. Assn. Am. Phys., 1933, **48**, 187.

PATHOLOGIC CHANGES IN THE HEART IN AURICULAR FIBRILLATION.*

By Henry K. Mohler, M.D.,
Associate Professor of Medicine, Jefferson Medical College,
and
Baxter L. Crawford, M.D.,
Associate in Pathology, Jefferson Medical College,
Philadelphia, Pa.

In auricular fibrillation of the chronic type—one of the common disturbances of the cardiac rhythm—there are generally evidences of myocardial damage. As in congestive heart failure, there are instances in which no organic changes are present, except hypertrophy. The most common structural changes found in the hearts of chronic fibrillators are mitral stenosis, coronary sclerosis and fibrosis of the myocardium. Yater,[1] in an excellent and the latest review of the literature, including 29 cases of his series studied microscopically, states that no distinctive lesion characteristic of auricular fibrillation could be recognized. It is difficult to make a postmortem diagnosis of the existence of auricular fibrillation during life from pathologic examination alone.

The circus movement theory is generally accepted as the explanation of the mechanism of this type of cardiac irregularity. The exact manner of onset in the human heart, however, is not known. The circumstances under which chronic fibrillation develops are numerous and variable.

In a previous communication, Mohler and Lintgen[2] reported on a clinical study of 220 cases of auricular fibrillation. It was quite obvious from this study and from other reports[3] that auricular fibrillation may either be associated with grave organic heart disease or with relatively unimportant functional disorders. In the present series only the 24 cases of auricular fibrillation which came to autopsy

* Read before Section of Medicine, College of Physicians of Philadelphia, November, 1932.

have been considered—and also for comparison of 7 cases of mitral stenosis without auricular fibrillation.

This arrhythmia may develop during or following attacks of acute infections such as tonsillitis, grippe and pneumonia. It commonly occurs in patients with mitral stenosis. It may follow severe physical or mental effort, trauma or conditions that increase the heart rate, as in exophthalmic or toxic adenomatous goiters. Often it is associated with degenerative lesions of the myocardium. It has occurred in apparently normal hearts.

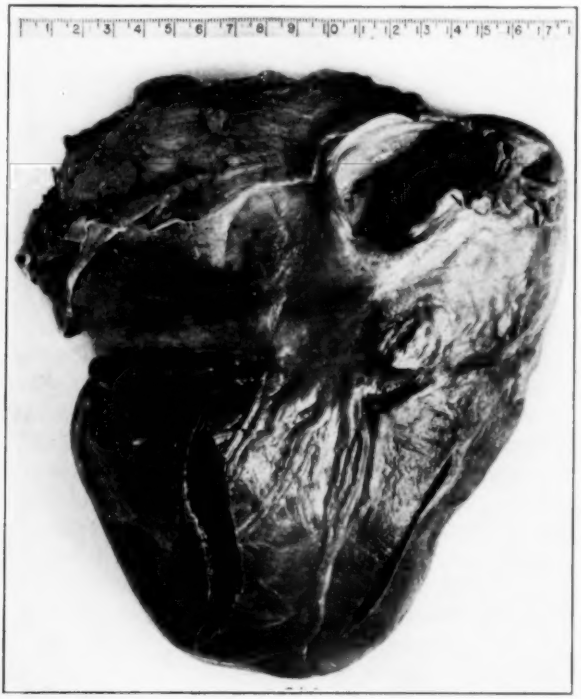


FIG. 1.—Case 10. Heart in a case of mitral and tricuspid stenosis with auricular fibrillation, to illustrate the enormous hypertrophy and dilatation, especially of the auricles.

An individual with a nervous temperament, with or without definite lesions in the heart, offers a favorable soil for this type of arrhythmia. Why in 2 patients with mitral stenosis, of apparently the same degree and under similar conditions, one should develop heart failure with a normal sinus rhythm and the other with auricular fibrillation, is yet to be explained satisfactorily.

It is quite obvious in this group that structural changes are present in the hearts of fatal cases with auricular fibrillation; but just as extensive and identical lesions are to be found in hearts without

auricular fibrillation. A number of selected rheumatic fever cases illustrate this point and many cases of coronary sclerosis, with fibrosis and infarction of the myocardium, occur without any change in the rhythm. These facts seem to indicate that changes in the rhythm may be associated with the lesions of the myocardium, or endocardium, plus some other unknown factor. It might be said that the frequent occurrence of auricular fibrillation in functional disorders of the heart could not be explained on this basis; but it is a fact that inflammatory and degenerative changes in the myocardium do occur in acute febrile diseases and other toxic disorders which, when the etiologic factor is removed, may retrogress without leaving any demonstrable structural change.

FIG. 2.—Case 5. Superior view of a heart in a case of auricular fibrillation, to illustrate the marked thickening and stenosis of the mitral and tricuspid valves.

Additional information upon the dynamics of the circulation of the blood with an increased knowledge of the chemical changes that take place in the auricular muscle and also outside of the heart ultimately may explain the reason for the development of auricular fibrillation. It is very desirable that the clinical, chemical and other laboratory findings should be studied in relation to one another, thereby correlating our knowledge on the subject.

Analysis of the important pathologic changes present in the hearts of chronic fibrillators has been undertaken to determine if there were any findings common within the rheumatic and arteriosclerotic groups, as well as in the fibrillator and non-fibrillator.

Method.—In all the chronically fibrillating cases which came to autopsy, the gross and the microscopic lesions were correlated. As the majority of the fatal cases of fibrillation occurred in mitral stenosis, all cases of marked mitral stenosis were studied for comparison. As previous studies (Yater[1]) have excluded the sinoauricular node as the site of the lesion, it was not considered necessary to make a special study of this node. All gross deviations from normal in the heart were recorded and a block of tissue was taken from the walls of each auricle and ventricle and one to include the main branch of the left coronary artery. The tissues from the auricles included the entire thickness of the wall. A number of sections were cut from different levels of each block of tissue so as to be sure to obtain representative sections for study. Sections, stained with hematoxylin and eosin and a fibrous tissue stain, were studied with special reference to the endocardium, myocardium, bloodvessels and epicardium.

The results of the histologic studies as well as the gross lesions are tabulated in Table 1.

Comparisons also have been made to ascertain how, if any, the pathologic changes present in the hearts of chronic fibrillators differ from those with normal rhythms in congestive heart failure resulting from rheumatic mitral stenosis. The number of hearts studied pathologically has not been large enough to permit statistical analysis, but it is evident that lesions common to their respective groups are present.

Why auricular fibrillation is seldom associated with syphilitic cardiovascular disease, with the active stage of rheumatic fever and with aortic valve disease (though common in mitral stenosis) remains an unsolved problem. Its rarity during the course of subacute bacterial endocarditis is also worthy of note. Study of the pathologic changes found thus offers no solution.

The table of probable etiology with accompanying pathologic lesions shows practically the same changes for the fibrillator and the non-fibrillator of the rheumatic group.

The average age at death was 31 years in the rheumatic and 33 in the non-fibrillator rheumatic group. The mitral valve was the one most frequently involved in both groups and the other valves in the same proportion.

Two of the rheumatic non-fibrillators had positive blood Wassermann reactions (one having both aortic and mitral lesions). It is probable that these 2 contracted syphilis after the onset of mitral disease. None of the fibrillators in either the rheumatic fever or the arteriosclerotic group gave evidence of having had syphilis. It is believed that syphilis is seldom responsible for causing stenosis of the mitral valve.

The average age at death in the two groups was about the same, 11 of the 14 rheumatic fibrillators having died of congestive heart failure and the other 3 of embolism. In the rheumatic non-fibrillator group approximately the same percentage died of congestive heart failure. The occurrence of embolism as a cause of death in 3 cases

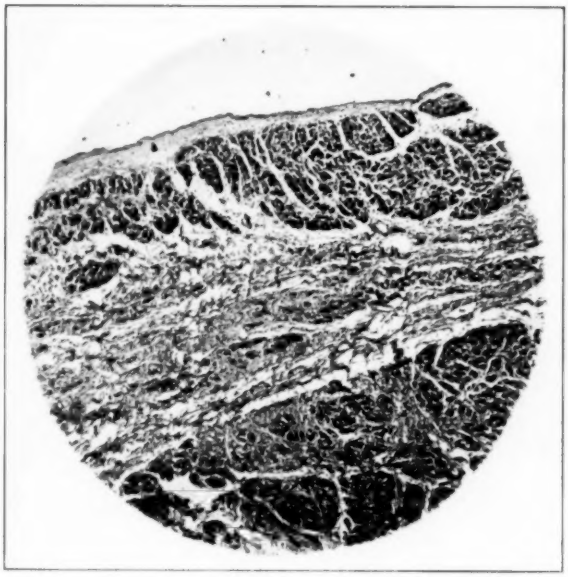


FIG. 3.—Case 5. Section of the left auricle in a case of auricular fibrillation, to illustrate slight fibrosis of the endocardium but marked fibrosis of the myocardium. (× 80.)

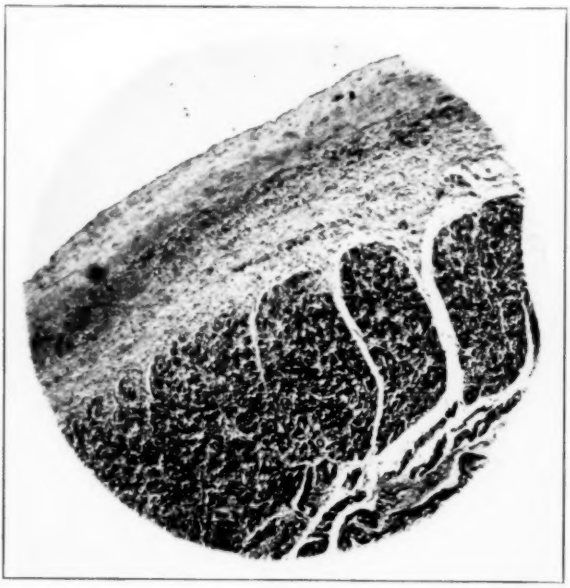


FIG. 4.—Case 7. Section from left auricle, to illustrate a marked thickening and inflammatory reaction in the endocardium and a slight fibrosis of the myocardium, in a case of auricular fibrillation. (× 89.)

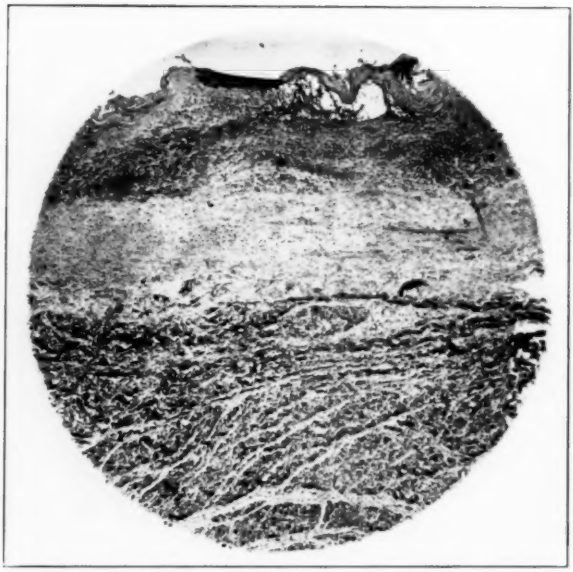


FIG. 5.—Case 30. Left auricle in a case of mitral stenosis without auricular fibrillation, to illustrate the marked thickening and inflammatory reaction of the endocardium and fibrosis of the myocardium. (× 56.)

TABLE 1.—LESIONS IN HEARTS OF CHRONIC FIBRILLATORS.

Case No.	Age.	Sex.	Mitral valve.	Aortic valve.	Tricuspid valve.	Auricular dilatation.	Condition of auric. myocardium.	Condition of auric. endocardium.	Thrombosis, auricles.	Other heart lesions.	Wt., gm.	Cause of death.
RHEUMATIC FEVER GROUP.												
1	21	M	Marked sten.	0	0	L.	L. degen.	L. fibr. and thick.	0	0	670	Cong. ht. fail.
2	22	M	Marked sten.	0	0	L.	L. fibr.	L. fibr. and thick.	L.	0	870	Cong. ht. fail.
3	31	F	Marked sten.	0	0	L.	L. fibr., sl.	L. fibr. and thick.	L.	0	?	Cong. ht. fail.
4	33	F	Mod. sten.	Mod. sten.	0	L. & R.	L. & R. calcif.	L. & R. fibr. and thick.	R.	L. vent. hypert. and dil.	800	Cong. ht. fail.
5	31	F	Marked sten.	0	Mod. sten.	L. & R.	L. fibr.	L. slt. fibr. and thick.	0	0	450	L. hemiplegia.
6	52	M	Marked sten.	Mod. sten.	0	L. & R.	0	L. fibr. and thick.	0	0	390	Cong. ht. fail.
7	31	M	Marked sten.	Mod. sten.	0	L. & R.	L. fibr., sl.	L. fibr. and thick.	0	Myoc. fib., L. vent. and cor. scler.	680	Cong. ht. fail.
8	25	F	Marked sten.	Mod. sten.	0	L.	0	0	0	0	430	Cong. ht. fail.
9	54	M	Marked sten.	Mod. sten.	0	L. & R.	L. fibr.	L. fibr. and thick.	0	0	450	Mesent. thromb.
10	46	M	Mod. sten.	0	Mod. sten.	L. & R.	L. fibr.	L. & R. fibr. and thick.	0	0	660	Thromb. basil. art.
11	37	M	Marked sten.	0	0	L. & R.	L. & R. degen. & fatty	L. fibr. and thick.	0	0	590	Cong. ht. fail.
12	34	F	Mod. sten.	0	0	L.	L. degen.	0	L.	0	550	Cong. ht. fail.
13	39	M	Marked sten.	Mod. sten.	0	L. & R.	L. & R. degen. & fibr.	L. fibr. and thick.	0	L. vent. hypert.	600	Cong. ht. fail.
14	18	M	Mod. sten.	Mod. sten.	0	L. & R.	L. & R. degen.	0	0	Chr. pericarditis	610	Cong. ht. fail.
15	39	M	Marked sten.	0	0	L. & R.	L. degen.	L. fibr. and thick.	0	0	720	Cong. ht. fail.
ARTERIOSCLEROTIC GROUP.												
16	73	M	Sclerosis	Sclerosis	0	0	0	0	0	Cor. scl., myoc. fib., L. vent.	600	Cong. ht. fail.
17	57	F	Sclerosis	0	0	0	L. fibr. and fatty	L. fibr. and thick.	R.	Cor. scl., fib., R. & L. vent.	700	Cong. ht. fail.
18	61	F	Sclerosis	0	0	0	0	0	0	0	290	Thromb. mes. art.
19	68	M	Sclerosis	0	0	0	0	0	0	Cor. scl., myoc. fib., L. vent.	370	Mil. abscesses.
20	61	M	0	0	0	0	0	0	0	Cor. sclerosis	330	Pneumonia.
21	52	F	Mod. scl. and sten.	0	0	0	0	0	0	0	350	Cong. ht. fail.
22	40	M	0	0	0	0	0	0	0	Cor. scl., myoc. fib., L. vent.	450	Cong. ht. fail.
23	64	M	Sclerosis	Sclerosis	Sclerosis	0	0	L. fibr. and thick.	0	Cor. scl., myoc. fib., L. vent.	?	Cong. ht. fail.
24	72	M	Sclerosis	0	0	0	0	0	0	L. vent. hypert., fib. and cor. scl.	550	Lobar pneum.
RHEUMATIC FEVER GROUP — **NON-FIBRILLATORS.**												
25	46	M	Mod. sten.	Marked sten.	0	L. & R.	0	L. sl. thick.	0	Hypert. and myoc. deg., L. vent.	780	Cong. ht. fail.
26	25	M	Mod. sten.	Mod. sten.	Mod. sten.	L. & R.	L. degen.	L. fibr. and thick.	0	0	510	Cong. ht. fail.
27	21	F	Marked sten.	0	0	L. & R.	L. & R. degen.	L. fibr. and thick.	0	0	370	Cong. ht. fail.
28	27	F	Marked sten.	0	Mod. sten.	L. & R.	L. & R. fibr.	L. & R. fibr. and thick.	0	Fibrosis, L. ventricle	680	Cong. ht. fail.
29	56	M	Mod. sten.	0	0	L.	0	0	0	Cor. scl., fibrosis, L. vent.	470	Rupt. duod. ulcer.
30	45	M	Marked sten.	Sclerosis	0	L.	L. fibr.	L. fibr. and thick.	0	0	410	Hemiplegia.
31	13	M	Marked sten.	0	Mod. sten.	L. & R.	L. & R. fibr.	L. & R. fibr. and thick.	0	Chr. pericarditis	470	Cong. ht. fail.

reduced the average age at death by 2 years as compared with the average age at death in non-fibrillators.

The occurrence of fibrotic lesions of the myocardium, especially in the left ventricle, was greater in the arteriosclerotic fibrillators than in the rheumatic.

The greatest difference in the pathologic findings was within the fibrillator group, namely, between the rheumatic fever and arteriosclerotic cases.

The absence of definite lesions other than thickening and sclerosis in the arteriosclerotic group is strikingly shown. Dilatation of the auricles was not present in this group. In only 1 of 9 of these cases was any histologic change noted in the auricular wall. Fibrosis and degeneration were present in the muscles of the auricles in 10 of the 14 rheumatic fibrillators and in 5 of the 7 rheumatic non-fibrillators.

The average weight increase in the hearts in the fibrillators of the arteriosclerotic group was less than in the rheumatic groups. This can be explained by the absence of hypertrophy of the heart either as the result of hypertension or marked valvular lesions. The first 2 of this series had evidence of hypertrophy as the result of hypertension. In this group, 7 of the 9 cases had definite coronary sclerosis. The greatest difference in the pathologic findings in these 3 groups of cases was not between the fibrillators and non-fibrillators, but between the rheumatic and arteriosclerotic type of fibrillators.

The pathologic changes present in the rheumatic groups were identical, whether auricular fibrillation was or was not present, even though the deaths were cardiac in origin.

Summary. 1. The hearts of 15 fibrillators and 7 non-fibrillators having an etiology of rheumatic fever and mitral valve lesions have been studied pathologically.

2. The hearts of 9 fibrillators with arteriosclerosis as the etiologic factor were also studied. They had sclerotic changes in mitral valves in 7 with apparently normal valves in 2 cases.

3. There were no pathologic changes common to all cases of auricular fibrillation found in this series of hearts. Nothing in this investigation indicates that the type of pathologic lesion found at autopsy can of itself be responsible for the onset and continuation of auricular fibrillation. Etiologic factors apparently determine the type of pathologic changes to be found in the heart to a greater extent than do the presence or absence of fibrillation.

REFERENCES.

1. Yater, W. M.: Arch. Int. Med., 1929, **43**, 808.
2. Mohler, H. K., and Lintgen, C. D.: Penna. Med. J., 1931, **35**, 68.
3. McEachern, D., and Baker, B. M., Jr.: Am. J. Med. Sci., 1932, **183**, 35.
Stroud, W. D., Laplace, L. B., and Reisinger, J. A.: Trans. Assn. Am. Phys., 1931, **46**, 52.

HEART DISEASE IN PREGNANCY. A PRELIMINARY REPORT.

By Arthur E. Lamb, B.S., M.D.,
ASSISTANT PHYSICIAN, THE BROOKLYN HOSPITAL; CHIEF OF PRENATAL CARDIAC CLINIC, THE BROOKLYN HOSPITAL DISPENSARY, BROOKLYN, N. Y.

(From the Medical Service of The Brooklyn Hospital, Dr. W. H. Lohman, Chief Attending Physician, and The Cardiac Clinic, under the direction of Dr. E. P. Maynard, Jr.)

A survey of the literature of heart disease in pregnancy and childbirth discloses a wide divergence of opinion as to its seriousness. This lack of uniformity of opinion led us to a study of the results being obtained in our own clinic and hospital service. Since 1926 there has been close coöperation between the obstetrical and medical departments, so that a woman entering the obstetrical clinic for prenatal care has her heart examined by the obstetrician on her first visit. If the slightest abnormality is detected she is referred to the prenatal cardiac clinic. The diagnosis of heart disease, therefore, is usually made early in her pregnancy, and she is then carefully supervised through her gestation. When the patient is admitted to the hospital the same close coöperation has been carried out.

Each patient on admission to the cardiac clinic has a careful history taken and a thorough physical examination of the heart and and orthodiagram, or a 6-foot Roentgen-ray plate, is obtained. The forms of the Research Committee of the New York Tuberculosis and Health Association are used. In this way we are usually able to separate the cases with functional murmurs from those with organic lesions. A final opinion is usually not made until a reëxamination after the laboratory studies are completed.

The difficulties of diagnosis of cardiac lesions are increased by pregnancy through such factors as the raised diaphragm, the rotation of the heart upward and to the left, the enlargement of the breasts and the more rapid pulse rate. Gammeltoff,[1] of Copenhagen, has shown that during pregnancy the condition of the normal heart may often simulate organic disease, even when not present. He studied 239 perfectly healthy pregnant women and found that during the final 2 months of gestation 16.3 per cent showed signs suggesting organic cardiac disease, such as fatigue, dyspnea on exertion, rapid pulse rate, extrasystoles, edema of the ankles, systolic murmurs, and accentuation of the pulmonic second sound. This was confirmed when, after pregnancy, it was impossible to detect the slightest evidence of a cardiac abnormality.

In Table 1, we have indicated the number of cases studied during the past 4 years. This shows that only 6.1 per cent of pregnant women have murmurs or signs referable to the heart, and that the

larger proportion are of the functional type. This figure agrees fairly well with the 7.5 per cent of Hamilton and Kellog,[2] of Boston. Our incidence of organic heart disease in pregnancy is 2.7 per cent. Sparks,[3] from a survey of the literature, reports an incidence of from 0.25 to 2.8 per cent.

TABLE 1.—ANALYSIS OF PREGNANT CARDIAC CASES.

	Admitted to obstetric clinic.	Referred to cardiac clinic.	Functional cardiac murmurs.	Organic heart disease.
1927	600	24	13	11
1928	477	29	17	12
1929	556	50	31	19
1930	560	32	23	9
Total	2193	135	84	51
Corrected totals: (One case diagnosis changed to non-organic postpartum),	85			50

Incidence of heart murmurs in pregnant women, 6.1 per cent.
Incidence of functional murmurs in pregnant women, 3.4 per cent.
Incidence of organic heart disease in pregnant women, 2.7 per cent.

Before considering the problem of organic heart disease, it would be well to amplify a little on functional heart murmurs, which as Gammeltoff[1] says are often included among the cases of heart disease treated in obstetrical clinics. These functional murmurs may be heard at all the valve areas—the largest percentage, nearly half, were detected at the apex, and about a quarter were heard at the pulmonic area. They varied in quality and intensity. We had 85 cases with these bruits, and 70 were confined in this hospital. All tolerated labor without the slightest evidence of cardiac strain. Following labor, 17 returned for reëxamination, and we were interested to find that in 15 of these, absolutely no murmur was then detectable. We are making an effort now to improve our follow-up in this type of case.

Thus it is clear that all heart murmurs do not mean heart disease, and it is only after careful study that the real can be separated from the spurious. Functional heart murmurs being without significance will in no way interfere with childbearing.

Organic heart disease, however, is an entirely different problem. Table 2 indicates the types of lesions encountered and their etiology. There were 50 cases from the clinic, and 20 were admitted to the hospital direct without being studied with the prenatal group. Rheumatic heart disease accounts for 90 per cent of these, mitral stenosis, with and without insufficiency, being the most frequent lesion (63 per cent). These figures tally fairly accurately with those of Breed and White[4] of Boston, and also Reid[5] who record a rheumatic incidence of slightly over 90 per cent. Hamilton and Kellog[6] found mitral stenosis more frequently (90 per cent). In Table 3 you will note that there were 44 patients with mitral stenosis who had 58 pregnancies, with decompensation in 20. From these

figures we may fairly state that about ⅓ of the patients with mitral stenosis may decompensate during pregnancy. The figures for the other types of lesions are too small to draw any general conclusions, but it would seem that uncomplicated mitral insufficiency is a rather harmless lesion. Halban[7] of Vienna emphasizes the importance of differentiating between insufficiency and stenosis of the mitral valve, and contends that the former is a relatively benign lesion, while the latter is an extremely grave complication of pregnancy. In Pardee's[8] series none of the cases of mitral insufficiency decompensated.

TABLE 2.—ORGANIC HEART DISEASE.

Number of cases, 1926 to 1931, hospital	20
Number of cases, 1927 to 1930, clinic	50
Mitral insufficiency	13
Mitral stenosis C and S, mitral insufficiency	44
Aortic insufficiency	5
Aortic insufficiency C, mitral stenosis and insufficiency	3
Fibrosis myocardium	3
Congenital heart disease—pulmonary stenosis	2
Etiology:	
Rheumatic heart disease	63
Luetic heart disease	1
Fibrosis myocardium—etiology unknown	3
Congenital heart disease	2

90 per cent heart disease in pregnancy—rheumatic.

TABLE 3.—RELATION OF VALVULAR LESIONS TO MORBIDITY AND MORTALITY.

Cases.	No.	Pregnancies.	Decompensation.	Died.
Mitral insufficiency (3 not confined in Brooklyn Hospital)	13	10	0	0
Mitral stenosis with and without mitral insufficiency (1 not confined in Brooklyn Hospital)	44	58	20	2
Aortic insufficiency	5	11	3	1
Aortic insufficiency with mitral stenosis and insufficiency	3	4	1	1
Fibrosis myocardium	3	3	1	1
Pulmonary stenosis	2	3	2	0

Within recent years the tendency has been more toward grouping cardiacs according to ability of the heart to withstand effort than according to structural damage. *Class 1:* Patients with organic heart disease able to carry on ordinary physical activity without discomfort. *Class 2:* Patients with organic heart disease unable to carry on ordinary physical activity without discomfort; (*a*) activity slightly limited; (*b*) activity greatly limited. *Class 3:* Patients with organic heart disease and with symptoms or signs of heart failure at rest, unable to carry on any physical activity without discomfort,[9] Hamilton[10] and many foreign observers, however, still group these cases on the basis of the anatomic lesion in the heart.

Pardee,[8] after studying the reaction of 106 pregnant cardiacs to an exercise test, found that Class 1 patients will not be expected to give trouble from cardiac insufficiency. Class 2 (*a*) patients prob-

ably will not give trouble. But there is a fair chance that a Class 2 (*b*) patient will decompensate. The Class 3 patients were not subjected to the test, as they were already decompensated, and he found their management difficult and the mortality high.

The patients studied in our clinic are classified functionally. Table 4 indicates the number of women in each class and the number who decompensated. We noted that 2 of the cases recorded as Class 1 and 3 of the Class 2 (*a*) decompensated, thus differing from Pardee. With this in mind, can we rely on a functional classification alone for a prognosis? We believe other factors should be considered as well. An analysis of the following cases may be helpful in arriving at a conclusion:

TABLE 4.—FUNCTIONAL CLASSIFICATION.

	No. Cases.	Preg.	Class 1.		Class 2 (*a*).		Class 2 (*b*).		Class 3.	Not class.	
			No failures.	Failures.	No failures.	Failures.	No failures.	Failures.	Failures.	No failures.	Failures.
Mitral insufficiency (3 not confined in Brooklyn Hospital	13	10	8	0	4	0	0	0	0	1	0
Mitral stenosis C and S, mitral insufficiency	44	58	15	2	16	3	7	4	11	9	0
Aortic insufficiency	5	11	3	0	2	0	1	0	2	3	0
Aortic insufficiency C and mitral stenosis and insufficiency	3	4	0	0	2	0	1	0	1	0	0
Fibrosis myocardium	3	3	0	0	2	0	1	1	0	0	0
Pulmonary stenosis	2	3	0	0	1	0	0	0	2	0	0
Decompensation	..	..	..	2	..	3	..	5	16		
Deaths	..	..	..	..	..	..	..	1	4		
Total	70*										

5 deaths; 66 cases; 7.5 per cent mortality; 31 per cent decompensated.

* 4 not confined in Brooklyn Hospital.

Case Abstracts. CASE 1.—Para II, aged 21, with mitral stenosis, who passed through a pregnancy in this hospital 3 years previously without any symptoms of cardiac insufficiency. During her 2d pregnancy was in Class 1 throughout until admitted in labor, with an acute upper respiratory infection. She had a precipitate delivery with cardiac decompensation 24 hours following. Discharged in good condition and when seen 3 months postpartum was reclassed as Class 1.

CASE 2.—Para I, aged 26, with mitral stenosis. In Class 1 throughout prenatal course, had an 11-hour labor, and showed signs of decompensation the morning following. Discharged in good condition and not seen again until 2 years later—she was 8 months pregnant. She was in Class 2 (*b*). She had an attack of paroxysmal tachycardia with decompensation, was admitted to the hospital and discharged 3 days later. She returned in labor, and during the first stage was slightly decompensated. However, she did not remain in the hospital until this had completely cleared and signed her release on the 10th day.

CASE 3.—Para III, aged 31. Mitral stenosis, 2 (*a*) classification. Went through pregnancy and labor without discomfort. She returned 1 year later Para IV and was again classed 2 (*a*). She was allowed to continue on

the basis of this classification. She showed signs of decompensation during a 14-hour first stage. We have a 2-year follow-up on this patient, and she is still 2 (*a*).

CASE 4.—Para V, aged 34. Mitral stenosis and insufficiency. A Class 2 (*a*) cardiac who reached only the 4th month, when she decompensated. She was hospitalized for 1 month with improvement. She was readmitted just before term, and had a Cesarean section with sterilization. During the following year she was admitted to the hospital 3 times, with cardiac decompensation, and was finally sent to Montefiore Hospital as a chronic invalid.

CASE 5.—Para I, aged 30. Mitral stenosis, was classified 2 (*a*) and became 2 (*b*) in later months of pregnancy. She was admitted before term with decompensation, and was digitalized with improvement. Cesarean section with sterilization was offered but the patient refused and signed her release.

In the first case, we had the added factor of infection with return to complete functional activity following. This case might not have decompensated if she had not had the acute respiratory infection.

The factor of age, duration of disease and extent of lesion enters into consideration in the other cases. The patient, aged 26, has maintained fair compensation for 2 years. The others had mitral stenosis of long duration. One is a chronic invalid, the other 2 left the hospital in bad condition.

From this we feel that other factors than functional classifications alone must be considered; namely, the age of the patient, the duration of the disease, the extent of the lesion, and the family environment. If these factors, along with functional classification, are considered, a more accurate prognosis can be given.

Decompensation occurred in 27 of the 66 patients confined in this hospital. We found that most of the decompensations occurred during the first pregnancy—perhaps because this hospital accepts for confinement mostly primiparas. The majority, 22 women decompensated before labor, with no definite relationship between the month of pregnancy and the onset of decompensation. Only 2 women showed the first signs of cardiac insufficiency during the first stage of labor, and 3 decompensated after labor, one 6 hours following and two 24 hours postpartum.

There were 5 deaths in our series. They are reported as follows:

Fatal Cases. CASE 1.—Para II, aged 29. Did not receive prenatal cardiac clinic care. Rheumatic heart disease, mitral stenosis with normal sinus rhythm, first pregnancy at 14 years. Decompensated at 5 months and admitted to the hospital. She was confined to bed and digitalized but compensation was not restored, congestive failure became progressively worse. She died 71 days after admission, $7\frac{1}{2}$ months pregnant.

Autopsy revealed a heart weighing 400 gm. with a markedly stenotic buttonhole mitral valve, admitting only the tip of the finger.

CASE 2.—Para II, aged 28. Did not receive prenatal cardiac clinic care. Rheumatic heart disease, aortic insufficiency, mitral stenosis and insufficiency with auricular fibrillation. First pregnancy at 24, decompensated at 3 months, was admitted to the hospital; compensation restored and had

abdominal hysterotomy and sterilization. She was discharged from the hospital 1 month later. Four months after discharge, was readmitted in acute cardiac decompensation and died 3 days later.

Case 3.—Para I, aged 22. Mitral stenosis, normal sinus rhythm. Clinic case. Class 1. Went through pregnancy without showing any signs of decompensation. She did not return to the cardiac clinic, but was readmitted at term as a private patient for a second pregnancy at 23, with findings of occasional sibilant râles at bases of lungs. No digitalis was given and labor was precipitant. First stage 15 minutes, second stage 19 minutes. Forceps control. She left the delivery room coughing. Six hours later she was cyanotic with pulmonary edema and died 33 hours after labor.

Case 4.—Para I, aged 20. Not seen in prenatal cardiac clinic. Rheumatic heart disease with mitral stenosis, who was admitted to the hospital decompensated at 4 months, was digitalized and had rest in bed for 18 days. She then had an abdominal hysterotomy and sterilization, and died 8 hours following with acute pulmonary edema.

Case 5.—A clinic case. Obese female, aged 39, Para I. She made one visit to prenatal cardiac clinic just 1 month before her admission to the hospital. She was seen by a cardiac clinic doctor whose diagnosis was fibrosis of myocardium, of unknown etiology. She was not classified. For some reason she did not return. She was admitted in labor and for 10 days on and off, according to the records, was in active labor for some part of the day with gradual rise in blood pressure and pulse rate. On the 10th day her labor became very active and auricular fibrillation began. She was seen by a medical consultant who suggested digitalization, but failure became progressively worse and she died on the delivery table with the baby *in utero*.

This was the only death in our clinic group and was a case incompletely studied and not supervised during the prenatal period.

Analyzing our 5 deaths, there were 2 cases in which death appeared to be due to the natural progress of the disease in the heart. The pregnancy, however, gave some additional burden, but even without it, the life expectancy was very limited. These 2 patients should not have been allowed to become pregnant. One death was following operation. The other 2 could perhaps have been prevented if they had had proper prenatal care. We feel that this is the most important point brought out in this study, and Table 5 will demonstrate this. In the clinic group only 23 per cent decompensated. Their symptoms were recognized early and they were admitted to the hospital in time to carry out the necessary treatment. Only 1 case died. This could probably have been prevented if she had been seen earlier in pregnancy and had been more carefully studied. The total mortality in the clinic group was only 2.2 per cent. In the other group the 11 patients who showed signs of cardiac insufficiency were all admitted in decompensation. Treatment was instituted but the mortality was 20 per cent. It is quite likely that if some of these women had been seen earlier their inadequacy to carry on would have been recognized in time to allow some surgical procedure to be successfully undertaken.

The value of prenatal care has been frequently emphasized in the literature. Hamilton and Kellog[6] by the organization of a prenatal clinic in Boston Lying-In Hospital were able to reduce their

TABLE 5.—COMPARISON OF MORBIDITY AND MORTALITY IN CASES STUDIED IN PRENATAL CLINIC AND THOSE ADMITTED TO HOSPITAL WITHOUT CLINIC CARE.

	Clinic cases.*	Cases without prenatal clinic care.	
	50	20	
4 not confined in Brooklyn Hospital	46		
Pregnancies*	64	25	
Decompensated	16	11	All Class 3 on admission
Deaths	1	4	
Per cent decompensated	23	44	
Mortality, per cent	2.2	20	
Fetal deaths	7	9	

* Readmission for subsequent pregnancies.

mortality from 21.2 to 16.2 per cent the following year. In the 4 subsequent years it ranged between 8.6 and 2.7 per cent. Corwin and Herrick[11] had a mortality of 5.8 per cent in their clinic group. It is obvious that pregnant cardiacs must be studied early in gestation and the risk properly evaluated from a careful history, physical examination, functional classification and an estimation of the degree of valvular and myocardial deficiency. If, from a consideration of these factors, there is then a likelihood that the cardiac condition will not allow the further strain, they can be referred to the obstetrician for interruption. If they are seen after the 4th month, when interruption is no longer a simple procedure, with proper management and hospitalization if necessary, they can usually be carried on until the response to medical treatment is such that they can withstand a carefully supervised labor or a Cesarean section. If under the best medical supervision they do not respond to treatment it is very likely that the degree of cardiac damage is so severe that they would not tolerate any surgical procedure. In this type of case it might be good judgment, as Corwin and Herrick[11] point out, to let Nature take its course.

Having considered the status of the cardiac mother in pregnancy and parturition, we were anxious to know what happened to her when she returned with her child to her home. Of the 46 clinic cases 23 returned for reëxamination and have been seen anywhere from 1 month to 5 years following their confinement. Only 3 of the mothers improved (13 per cent), 10 remained the same (43 per cent). From this we might state that about 56 per cent were not made worse by pregnancy. Ten (43 per cent) were worse following their pregnancy. Seven of these were badly decompensated patients. One died 4 months after an abdominal hysterotomy and sterilization and 6 are chronic invalids unable to carry on any physical activity.

Our results are not as favorable as those of Corwin and Herrick[11] who report that 66 per cent of their cases became free from symptoms following pregnancy, while 35 per cent complained of varying degrees of cardiac strain.

Summary. 1. The incidence of cardiac murmurs in pregnant women in our series was 6.1 per cent. Of these, 2.7 per cent had

organic heart disease, while 3.4 per cent had functional murmurs only and no detectable lesion.

2. The importance of recognizing functional murmurs has been pointed out. None of these patients showed the slightest evidence of cardiac strain during pregnancy, and our follow-up shows that nearly all of these functional murmurs disappeared after pregnancy.

3. Rheumatic heart disease causes about 90 per cent of the heart lesions in pregnant women.

4. The most frequently observed lesion is mitral stenosis with or without insufficiency.

5. One-third of our cases of mitral stenosis decompensated, while no case of uncomplicated mitral insufficiency decompensated, demonstrating the importance of differentiating between these two lesions.

6. The functional classification of pregnant cardiacs has been considered and it was noted that 5 cases out of Classes 1 and 2 (*a*) decompensated, which is at variance with the work of Pardee who claims that Classes 1 and 2 (*a*) have an excellent prognosis.

7. Other factors, in our opinion, must be considered in addition to the functional classification, such as the age of the patient, the family environment, the duration of the heart disease, and the extent of valvular damage.

8. Most of our cases that decompensated did so before the onset of labor and there was no relationship demonstrated between the month of pregnancy and the onset of decompensation.

9. Our mortality was 7.5 per cent which falls within the mortality range of 5 to 10 per cent as reported by reliable observers. Two of these deaths were probably preventable.

10. Consideration of the mortality of the cases having prenatal care and those who did not, shows a death rate of 2.2 per cent in the former and 20 per cent in the latter, thus demonstrating the importance of prenatal care.

11. The limited follow-up showed that 56 per cent were not worse following pregnancy, while 43 per cent were. The need for further follow-up study to determine what happens to the cardiac mother and her child after the lying-in period is obvious.

REFERENCES.

1. Gammeltoff, S. A.: Surg., Gynec. and Obst., 1928, **46**, 382.
2. Hamilton, B. E., and Kellog, F. S.: Am. J. Obst. and Gynec., 1927, **13**, 535.
3. Sparks, T. P.: South. Med. J., 1929, **22**, 571.
4. Breed, W. B., and White, P. D.: Boston Med. and Surg. J., 1923, **188**, 984.
5. Reid, W. D.: J. Am. Med. Assn., 1930, **95**, 1468.
6. Hamilton, B. E., and Kellog, F. S.: J. Am. Med. Assn., 1928, **91**, 1942.
7. Halban, J.: Wien. klin. Wchnschr., 1928, **41**, 628; Abstract, J. Am. Med. Assn., 1928, **91**, 216.
8. Pardee, H. E. B.: Am. J. Obst. and Gynec., 1929, **17**, 255.
9. Criteria for the Classification and Diagnosis of Heart Disease, New York Tuberculosis and Health Association, 2d ed., 1929, p. 90.
10. Hamilton, B. E.: New England J. Med., 1928, **198**, 292.
11. Corwin, J., and Herrick, W. W., Valentine, M., and Wilson, J.: Am. J. Obst. and Gynec., 1927, **13**, 617.

ANEMIA AS THE CAUSE OF ANGINA PECTORIS IN THE PRESENCE OF HEALTHY CORONARY ARTERIES AND AORTA: REPORT OF CASE.

By Albert H. Elliot, M.D.,
Associate Physician, Cottage Hospital,
Santa Barbara, Calif.

(From the Department of Clinical Research.)

Herrick and Nuzum[1] in 1918 first called attention to the combination of anemia and angina pectoris 4 times in 200 patients with angina pectoris. Three of these patients died, 1 in an anginal seizure, but no autopsies were obtained. In 1926 Coombs,[2] in a series of 36 patients with pernicious anemia, found this combination in 8. One of these patients died and at autopsy "diffuse atheroma" of the aorta was found. The coronary arteries were not mentioned. At this time Cabot's book[3] on heart disease appeared, in which he made this statement: "I have seen 3 cases of intense and typical angina associated with pernicious anemia and without coronary change. One showed moderate sclerosis of the aorta, the others none. All were strictly dependent on exertion and relieved by rest. Such cases, like those seen in convalescence from pneumonia and other infections, make us skeptical of any etiology based wholly on organic and permanent changes either in the coronaries or in the aorta."

Herrick again[4] in 1927 described 3 more instances, in 2 of which necropsy disclosed arteriosclerotic change of the coronary arteries. In his review of the literature to that year Herrick remarked that the combination of these two diseases had been infrequently noted, and quoted the opinion of Bullrich, who had reported 7 cases, to the effect that there is a substratum of coronary disease which can be made partly answerable for the presence of the anginal syndrome. During the same year Willius and Giffin[5] reviewed 1560 cases of pernicious anemia encountered at the Mayo Clinic. The anginal syndrome was present in 43 (2.7 per cent) of these patients, in only 1 of whom a postmortem examination was made. Unfortunately, permission to remove the heart was not granted and the smallness of its size was the only feature remarked upon. In discussing Herrick's paper, however, Giffin mentioned one case in which at autopsy normal coronary arteries but fatty change of the myocardium were found. A detailed description was not given.

The only other pertinent report which I have encountered is that of Reichel[6] who, in a series of 114 instances of pernicious anemia, found angina pectoris present in 3. Two of these patients came to necropsy. The heart of 1 had dilated chambers, normal aorta and valvular apparatus and, microscopically, vacuolization of the muscle bundles. The second patient had arteriosclerosis of the aorta, fatty change of the left ventricle and an area of myomalacia. The coronary arteries were not specifically mentioned in either instance,

but the presence of myomalacia in the second suggests the presence of coronary disease.

From the foregoing it is evident that the occurrence of angina pectoris in patients with anemia is more than a coincidence. If we believe that acute disproportion between the coronary flow and the metabolic demands of the myocardium is the underlying cause of the anginal seizure, it would appear that anemia might further this occurrence in the presence of diseased coronary arteries, or that, in the absence of coronary disease, it might cause such a disproportion in the event that the adaptive physiologic limit of the coronary flow were exceeded. Proof of this latter occurrence would demand the clinical presence of well-defined angina pectoris in a patient with anemia and the absence of gross or microscopic changes of the coronary arteries at autopsy. If likewise the aorta were unchanged, we should have convincing evidence that angina pectoris may depend, in some instances at least, upon altered functional balance rather than upon structural disease. Since, with the exception of the cases briefly mentioned by Giffin and by Cabot, a convincing demonstration of this occurrence has not been offered, the following report may be of interest:

Report of Case. Mrs. I. W., an American housewife, aged 55, complained of angina pectoris, nosebleeds and anemia. The familial background was good except for the death of her mother from a stroke at 65. As a child, the patient had whooping cough, scarlet fever and "growing pains" over a period of 1 year. At 17 she had typhoid fever; at 27, pneumonia; and at 35, diphtheria. She had recovered uneventfully from these illnesses. She had had one uneventful pregnancy 26 years ago. There was no history of glossitis or neuromuscular disturbance. Her blood pressure had always been low. The patient's health had been excellent until 7 years ago. At that time, while working hard on a farm, palpitation appeared and became so severe that a 3 weeks' rest in bed became necessary, during which it gradually quieted. Shortly after this her gall bladder was removed because of chronic indigestion. She soon felt well and could walk 7 miles without cardiac symptoms. Four years later she had repeated severe nosebleeds and became "very anemic." Black and blue spots spontaneously appeared over the left breast and arm. A nasal operation was done without benefit and a tonsillectomy was decided upon. As she was about to enter the operating room she had a sudden viselike pain in the pit of the stomach which spread up into the neck with "contraction" of the throat muscles, and down the inner side of the left arm to the elbow. There was profuse perspiration and difficulty in breathing. Inhalation of amyl nitrite brought immediate relief. She had repeated seizures of this character during the next 2 days. The operation was not done. She gradually returned to her household duties, but overexertion was sure to bring sensation of faintness, and on 5 or 6 occasions during the following 2 years the anginal seizures recurred. She had nosebleeds at intervals of 4 or 5 months during this time and remained anemic in spite of medication. Four months ago the nosebleeds occurred more frequently and in the course of 6 weeks she had as many anginal attacks. They were relieved by nitroglycerin, which she kept constantly available. Three weeks before I saw her she developed cough and fever, diagnosed influenza, and while in bed had as many as 6 anginal attacks in 1 day. There was also an epistaxis with the loss of

"a quart" of blood. The anginal seizures became so severe that a fatal termination was feared. She entered the Cottage Hospital, where she remained until her death 1 month later.

Physical Examination. The patient was a well nourished and developed woman sitting semiupright in bed, breathing easily. She was intelligent, coöperative and cheerful. Cyanosis was absent. There was a generalized yellowish pallor of the skin; the scleræ were white. The fundi showed pallor only. There was a perforation of the nasal septum from a previous operation. The buccal membrane was pale, the tongue was not smoothed nor were the papillæ atrophied. The thyroid gland was not enlarged. The carotid pulsations were vigorous, the venous pulsations not remarkable.

The pulse was regular, of low volume, rate, 90. The blood pressure: 100 mm. systolic, 50 mm. diastolic. Duroziez's sign and capillary pulsation were not present. The accessible arteries were soft. The apex beat of the heart was felt as a diffuse, feeble thrust in the 5th left interspace 1 cm. lateral to the midclavicular line. The left cardiac border was aortic in shape to percussion, the right was outlined 2 cm. lateral to the sternal border in the 4th and 5th interspaces. There was no substernal or increased aortic dullness. The heart sounds at the apex were feeble, the first merging into a rough systolic murmur which was transmitted to midaxilla. The sounds at the base were distant. In the 2d left interspace at the sternal border a localized, inconstant soft diastolic murmur was heard immediately following the pulmonic second sound.

The remainder of the physical examination was non-informative.

Laboratory Data. The blood Wassermann reaction was negative; hemoglobin, 57 per cent (Sahli); red blood cells, 3,120,000 per c.mm.; leukocytes, 6300, with a normal differential count and no shift of the Schilling index. The stained smear showed moderate poikilocytosis and anisocytosis with tendency to megalocytosis. The platelets numbered 287,000 per c.mm. There was no alteration of the bleeding or clotting time. Agglutination tests for B. typhosus and B. melitensis were negative. An alcohol fractional test meal disclosed an achlorhydria.

The electrocardiogram (Fig. 1) showed a flattening of T in Lead I, with slight depression of the R–T segment below the isoelectric line in Leads I and II. On fluoroscopic examination of the chest slight haziness was apparent at the right lung base. The heart was enlarged to the left and slightly to the right and was aortic in shape. The apex was rounded. The aorta was not widened. Orthodiagraphic measurement gave a transverse cardiac diameter of 14.25 cm., exceeding by 25 per cent her calculated normal of 11.4 cm. (tables of Heiges and Eyster).

Course. Throughout a month's observation, her temperature varied daily from 99° to 101–102° F., the peak occurring in midafternoon. The pulse ranged between 80 and 90 beats per minute. Shortly after hospital entry petechiæ appeared over the upper trunk and mucous membranes. Because of these findings, a diagnosis of bacterial endocarditis was entertained, but repeated blood cultures gave no growth. The cardiac findings remained unaltered, except that the diastolic murmur was variable in intensity and frequently inaudible. She experienced no further anginal attacks. During the second week she was given 5 injections of liver extract (Lederle) intramuscularly, together with iron and ammonium citrate, 10 gr. (0.6 gm.), three times daily. The red cells increased from 3,120,000 to 4,000,000 per c.mm., while the hemoglobin remained unchanged.

After 3 weeks in the hospital she had improved materially in strength, when suddenly an intestinal obstruction developed. At operation a peritoneal adhesion causing a complete small bowel obstruction was freed. The postoperative course was uneventful for 3 days, when congestive heart failure became manifest, leading to a fatal termination on the 7th postoperative day.

Necropsy was performed 5 hours after death. The anatomic diagnoses were: surgical wound of the abdomen; hypertrophy and dilatation of the left heart; acute fibrinous pericarditis; passive congestion of the viscera; edema of the lower extremities and posterior body wall.

The heart, with 5 cm. of attached aorta, weighed 601 gm. The epicardium was lusterless and covered with a shaggy fibrinous exudate. Epicardial fat was not increased. The left auricle was not dilated, the right only slightly. The left ventricle was rounded and firm and the wall was 2.5 cm.

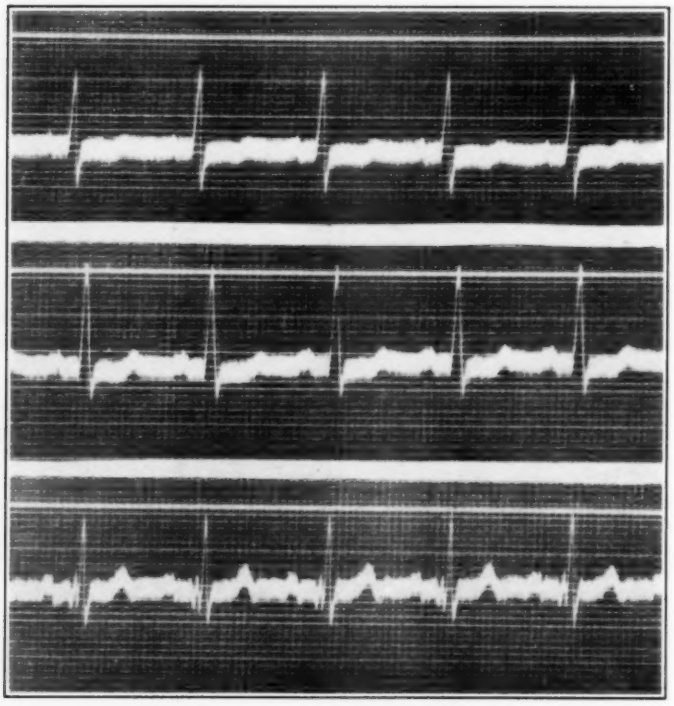


FIG. 1.—Electrocardiogram taken on hospital entry. The leads are arranged in standard order from above downward.

in thickness at a point midway between apex and base. The softer wall of the right ventricle, measured similarly, was 5 mm. There was no disease of the endocardium or valvular apparatus. Tigroid marking was absent. The aortic ring had a circumference of 7 cm., and was not patent to water test; mitral 8.5 cm. with slight nodular thickening at line of closure. There was slight lipoid flecking of the ascending aorta. The coronary arteries gave the appearance of extreme dilatation and showed no gross changes except occasional flecks of intimal lipoid deposition on the main stems. Particular attention was paid to the smaller radicals which were widely open and not diseased. The myocardium was uniformly pale but firm.

Microscopic study of the heart muscle (Dr. Richard Evans) disclosed a moderate widening of the fibers but no fibrosis, cellular infiltration or fatty change. The walls of the coronary arterioles were of normal size and

structure and patent throughout. There was a slight increase in delicate perivascular fibrous tissue, such as would be expected at this age.*

Discussion. The history suggests a definite correlation between repeated episodes of epistaxis and the occurrence of anginal attacks as extending over a period of years. The angina for the most part was produced by exertion until the onset of a febrile illness, together with further loss of blood, when it occurred while at bed rest. At autopsy a pronounced cardiac hypertrophy was found in the absence of the usual causes for such a condition. Antecedent hypertension could be excluded on the basis of the patient's statement that her systolic pressure had never exceeded 110 mm. Hg on repeated examinations, and by the fact that there was no arteriosclerosis of the retinal vessels. While the diagnosis of the underlying condition is not entirely clear (pernicious anemia is extremely likely, but post-hemorrhagic aplastic anemia is possible), I believe the foregoing facts can be explained on the basis of certain physiologic conceptions.

It seems well established that the cardiac output is increased in anemia. Fahr and Ronzone,[7] studying a patient with a hemoglobin percentage of 12 per cent and a red cell count of 550,000 per c.mm., found that the output was increased to 250 per cent of normal. The calculated coronary flow of this patient in the resting state equalled that present normally in response to severe exertion. Increased cardiac output has likewise been found in lesser degrees of anemia but is not necessarily proportionate to it, probably varying with the causative clinical condition.[8] Fahr and Ronzone concluded that the extra work of the heart in anemia may cause hypertrophy. This in turn may demand an increase in coronary flow to insure adequate nutrition of the myocardium if we assume with Fahr[9] that the hypertrophied muscle cell increases its volume as the increase in the square of its diameter, but increases its surface area only as the increase in actual diameter, thus putting it at a disadvantage in the exchange of nutritive substance and waste products.

These concepts suggest that in anemia the adaptive limit of the coronary flow may be easily exceeded, particularly if myocardial hypertrophy be present, under circumstances in which the physiologic demands placed upon the heart muscle are increased, *e. g.*, exertion, fever.

The probable course of events in this patient now becomes clear. To insure adequate circulation, her heart responded to the presence of chronic anemia by increased cardiac output signalized morphologically by hypertrophy of the muscle fibers. The stress of exertion, together with acute blood loss, was sufficient to precipitate myocardial ischemia with resultant angina pectoris. It does not seem necessary to invoke the hypothesis of either "coronary spasm"

* Heart sections forwarded to the Editor showed no evidence of coronary or myocardial disease.—The Editor.

or overstretching of the arterial walls as an explanation of the anginal seizures. With the occurrence of a febrile illness, the circulatory demands were increased to the extent that the coronary flow became inadequate even while at bed rest. There resulted angina of decubitus.

One other point should be noted. The electrocardiogram showed a definite alteration of the R–T segment which in this instance could not be attributed to organic disease of the myocardium or coronary arteries. As anemia *per se* apparently does not bring about alteration of the electrocardiogram,[10] a functional disturbance which resulted from myocardial anoxemia may reasonably be invoked as the explanation, particularly since similar changes in the electrocardiogram have been produced both in the experimental animal by asphyxia[11] and in persons with angina pectoris subjected to oxygen deficiency.[12]

Summary. 1. A 55-year-old woman with chronic anemia and repeated expistaxes had attacks of angina pectoris over a period of 3 years which became extremely severe with the occurrence of a febrile illness.

2. At necropsy an hypertrophied but otherwise normal heart was found. The coronary arteries were thin-walled and dilated, detailed study revealed no lesions in their walls other than occasional flecks of lipoid on the intima; the aorta was unchanged.

3. The physiologic evidence is reviewed, which indicates that anemia, by increasing cardiac output, may cause myocardial hypertrophy; that under these circumstances the adaptive limit of the coronary flow may be reached in the resting state and easily exceeded under additional physiologic circulatory burden; and that the resultant myocardial ischemia might express itself as an anginal seizure.

4. It is suggested that such a mechanism could well explain both the clinical and pathologic findings in this case.

5. This study demonstrates that angina pectoris may occur in the absence of disease of the coronary arteries, myocardium or aorta.

REFERENCES.

1. Herrick, J. B., and Nuzum, F. R.: J. Am. Med. Assn., 1918, **70**, 67.
2. Coombs, C. F.: Brit. Med. J., 1926, **2**, 185.
3. Cabot, R. C.: Facts on the Heart, Philadelphia, W. B. Saunders Company, 1926, p. 555.
4. Herrick, J. B.: Trans. Assn. Am. Phys., 1927, **42**, 23.
5. Willius, F. A., and Giffin, H. Z.: Am. J. Med. Sci., 1927, **74**, 30.
6. Reichel, J.: Wien. Arch. f. inn. Med., 1929–1930, **18–19**, 241.
7. Fahr, G., and Ronzone, E.: Arch. Int. Med., 1922, **29**, 331.
8. Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C Thomas, 1932, p. 239.
9. Fahr, G. E.: J. Am. Med. Assn., 1923, **80**, 981.
10. Reid, W. D.: Ibid., p. 534.
11. Criep, L. H.: Arch. Int. Med., 1931, **48**, 1098.
12. Dietrich, S., and Schwiegk, H.: Klin. Wchnschr., 1933, **12**, 135; Abstract, J. Am. Med. Assn., 1933, **100**, 1073.

CHRONIC HEREDITARY HEMOLYTIC JAUNDICE.

WITH A REPORT OF 8 CASES AND NOTES ON MEASUREMENT OF THE SIZE OF ERYTHROCYTES.

BY WILLIAM FITCH CHENEY, M.D.,
EMERITUS CLINICAL PROFESSOR OF MEDICINE,

AND

GARNETT CHENEY, M.D.,
ASSISTANT CLINICAL PROFESSOR OF MEDICINE, STANFORD UNIVERSITY SCHOOL OF MEDICINE, SAN FRANCISCO, CALIF.

RECENTLY an unusual group of patients, comprising three generations with the same disease, were brought to our attention by Dr. Max M. Goldstein, their family physician. We have had opportunity to study 5 members of this family: a grandmother, her son and his wife and their 2 children; and careful examination of these people led to the discovery in 3 of them of absolutely conclusive evidence of chronic hereditary hemolytic jaundice. This evidence was as follows:

Case Reports. CASE 1.—Mrs. M., aged 67, was born in Nova Scotia of Scottish parents. She said her own mother, now dead, had a large spleen and a yellow color of the skin all her life; likewise her brother, who is still living, but not available for study. Mrs. M. said she herself had always been more or less yellow; never normal in color. She had known also for the past 30 or 40 years that she had a large spleen, though this varied in size at different times. Nevertheless these peculiarities had never made her ill or caused her pain or any marked incapacity. She had always had to work hard and had always been able to do so. She had borne and raised 4 children successfully. The only serious event in her life was the removal, 17 years previously, of a gall bladder packed with stones. This relieved her of discomfort but did not decrease her jaundice or the size of her spleen.

Physical Examination. A small, poorly nourished, sallow and mildly icteric woman. Her liver was not increased in size and its lower border was not palpable. The spleen, however, was much enlarged, extending slightly below the navel and as far inward as the middle line of the abdomen. It was firm, smooth, not tender. No other abnormalities of importance were found in the physical examination. The blood count showed only 30 per cent of hemoglobin and 1,930,000 red cells, though the patient had no complaint to offer even after a long journey. The white count was 6050, with a practically normal differential. The red cells showed marked anisocytosis but very slight poikilocytosis and no polychromatophilia. The majority of the red cells were microcytes, showing an average diameter of only 6.5 μ as compared with the normal 7.5. Reticulocytes, however, did not exceed 1 per cent. Increased fragility was shown by the fact that hemolysis began at 0.5 per cent salt solution and was complete at 0.46 per cent as compared with a normal control of 0.4 and 0.34. The icterus index was 35 and the direct van den Bergh was negative.

CASE 2.—Mr. M., aged 40, a son of the preceding, was born in North Dakota. He had been married for 8 years and had 2 children. He complained only of lack of strength and said he had never been strong. All his life he had been more or less jaundiced, either sallow or at times defin-

itely yellow. He never had the stamina "to put anything through," as he expressed it. Riding horseback, any hard work or heavy lifting always made him worse. A very little thing would make his health "fall down" and then it took a long time to build up again. This patient was the one who first consulted Dr. Goldstein and whose condition led to the discovery of the others in the family group. He likewise had had his gall bladder removed in 1925; no stones were found, only a dark, thick, tenacious bile. This operation relieved the discomfort over his liver and in his epigastrium

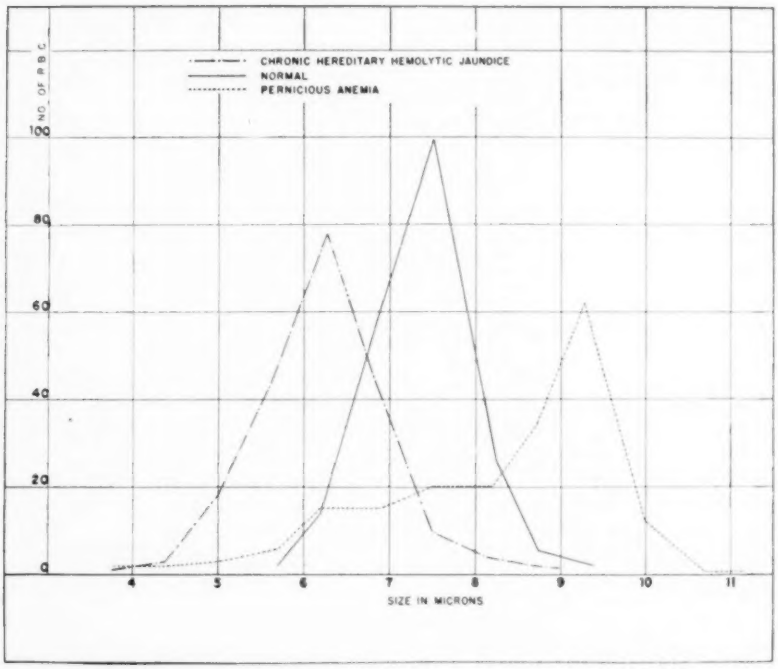


FIG. 1.—Price-Jones curves showing the normal, the shift to the left in microcytosis (Case 1), and the shift to the right in a typical case of pernicious anemia with marked macrocytosis.

but did not remove his jaundice or weakness or decrease the size of his spleen. On physical examination, this man was small, pale and slightly icteric. His liver was not enlarged and its lower border was barely palpable below the ribs. The spleen, however, extended below the level of the navel and as far inward as the middle line. It was firm, smooth and not tender. No other abnormality was found. His blood count showed 62 per cent hemoglobin and 3,320,000 red cells, with marked anisocytosis and many microcytes with an average diameter of 6.5 μ. There was no increase in reticulocytes. The white count was 7950 and the differential count normal. Resistance to osmosis was decreased, hemolysis beginning at 0.5 per cent and complete at 0.38 per cent. The icteric index was above 40 and the direct van den Bergh negative. The urine was distinctly red but contained no bile.

CASE 3.—This patient, aged 4, was the son of Case 2. He had always been pale and sallow from his birth and never seemed quite healthy; but

on the other hand he had never been seriously ill. For 2 years it had been known that he had a large spleen. On physical examination the peculiar sallow anemia was at once apparent but the boy was well nourished. His spleen was palpable as low as the navel and by percussion extended high in the axilla. No other abnormality was found on physical examination. The blood count gave only 45 per cent of hemoglobin and 2,760,000 red cells. There was pronounced anisocytosis but no increase in reticulocytes. The red cells averaged 6.3 m. in diameter. The white count was normal. Hemolysis of red cells began at 0.5 per cent and was complete at 0.38. The icterus index was 30 and the direct van den Bergh negative.

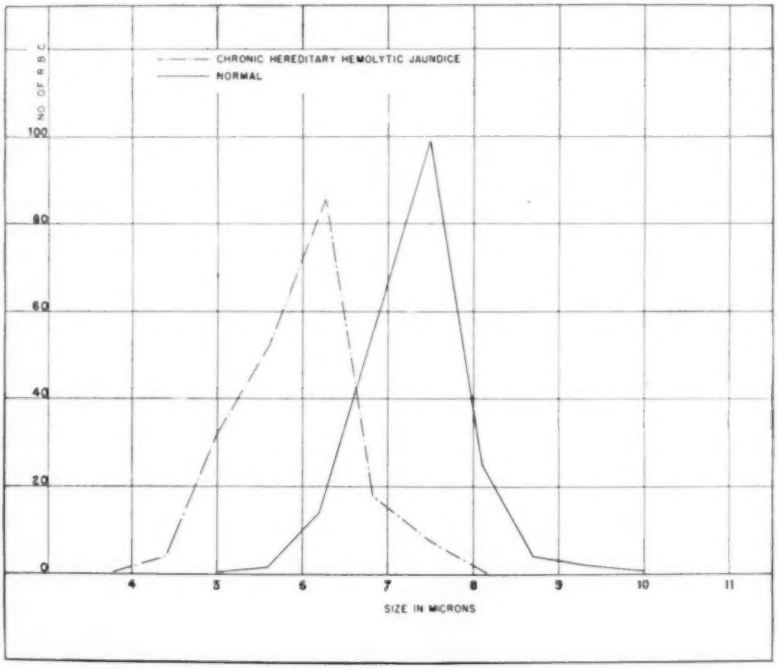


FIG. 2.—Price-Jones curve of Case 3, showing extreme microcytosis, compared with a normal curve.

Other Members of the Family. By contrast with these figures, the other son, aged 6, with every appearance of good health and with no enlarged spleen, showed 70 per cent hemoglobin, 4,030,000 red cells, no anisocytosis, hemolysis beginning at 0.38 and complete at 0.34 and an icterus index of 6. The mother of the 2 children was likewise normal in every respect, on physical examination and by all blood tests. This rare group of patients prompted an investigation of the literature of the subject and the result is the following review of present-day knowledge of the disease in question.

History. In 1900, Minkowski[1] described a new form of disease, of which the outstanding features were heredity; chronic icterus, without bile in the urine; persistent enlargement of the spleen; onset of the symptoms at birth or in early childhood, lasting for

years and not as a rule shortening life. A few similar cases had been published here and there previous to 1900. In particular the contribution of Hayem[2] to the subject in 1898 deserves mention; for he had presented then the history of 5 cases observed, in whom he described as the four main characteristic features, chronic icterus, large spleen, anemia and acholuria. After 1900 many others reported its occurrence and knowledge regarding it rapidly increased. The next great advance in the understanding of the condition was made by Chauffard[3] and his pupils, who first directed attention to the excessive fragility of the red blood corpuscles and the diminution of their average size in this disease, emphasizing the importance of hemolysis in the production of the icterus. The priority of description rightly assigned to Minkowski, together with the later valuable contributions by Chauffard, justify the designation of the condition as the Minkowski-Chauffard disease. A little later, in papers published during 1907 to 1911, Widal[4] and his pupils challenged the original conception of Minkowski that all cases were hereditary; and contended that the disease might sometimes be acquired. Whether it is justifiable to admit the existence of such acquired cases has been a matter of controversy ever since and there seems at present good reason to doubt it. But what are so described have become known as the Widal-Abrami group. Credit for the first adequate description of the disease published in American literature belongs to Tileston and Griffin[5] (1910). In 1922 Meulengracht[6] published the most comprehensive monograph on the subject that had appeared up to that date and, since then, the most noteworthy contribution to the subject has been that of Gänsslen,[7] whose views are generally accepted today.

Incidence. The disease is not a common one, and only a few individuals have been able to observe and study any considerable number of patients. Yet physicians all over the world have reported isolated cases which now total several hundred. Minkowski based his original paper on the personal investigation of 8 patients. Chauffard and Widal made their classical additions to the subject, after research upon 1 patient here, another there and altogether only a limited number. When Meulengracht published his monograph in 1922 he was able to find in all Denmark at that time only 34 patients in whom he could personally verify the diagnosis with sufficient certainty. Gänsslen,[7] however, reporting in 1927 his experience with the disease, states that he had seen to that date about 120 cases with definite and typical symptoms and signs, besides numerous compensated ones that were less easily distinguished. He attributed this large material observed in his clinic at Tübingen to a regional distribution of the disease, and is convinced that South Germany contains more of these patients than adjacent regions. His opportunity for the study of chronic hereditary hemolytic jaundice, therefore, has probably been greater than

that of any other individual research worker and his views are correspondingly valuable. From the extensive bibliography on the subject it appears that the disease is not seen as often in this country as in Europe; though less familiarity with the subject may be chiefly accountable.

Etiology. There has never been any doubt since the disease was first recognized that at least the Chauffard-Minkowski variety runs in families, may appear in several successive generations and can be transmitted to the children by either parent. This is well exemplified by the cases described in this report. The only question has been whether or not all cases are accounted for by heredity. Gänsslen's conclusion, based on his large experience, is that what patients inherit is a "hemolytic constitution." In some this manifests itself at birth (*i. e.*, congenital); in others it does not appear until early childhood; in still others not until adult years. Finally, it may never appear at all during the patient's life in such outspoken form as to lead to its recognition. Gänsslen believes that the so-called acquired cases are born with this "hemolytic constitution" and that any sort of disturbance later on, such as unfavorable conditions of living, acute or chronic infections or trauma may destroy the compensation by which health was maintained in spite of their defect and so precipitate the symptoms and signs of chronic hemolytic jaundice. There is thus no distinction between hereditary and acquired cases as regards their etiology except that the latter require some additional factor to bring out the latent fault.* During the period of latency even the carrier may not note any signs of ill-health and the physician likewise can discover no abnormality except by the most painstaking clinical and laboratory investigations. When the patients with a hemolytic constitution escape any characteristic manifestation of it throughout life, the defect may nevertheless be transmitted to their offspring and in them the disease may definitely appear. Then the fact of heredity may be overlooked and the case seem to be acquired. The fundamental feature of what Gänsslen calls the hemolytic constitution is a lack of capability of the blood forming organs to supply perfect red cells; and this congenital inferiority or debility of the erythrocytes results in their constant destruction, to a greater or less degree, but always in excess of the normal physiologic process.

Pathology. The changes in various organs found in association with this disease are fairly well established, in spite of relatively few autopsy reports. (1) *The liver* naturally calls for consideration. Anatomic changes in it are slight or absent altogether. It rarely is enlarged, either during life or at autopsy. In some few instances a real hypertrophy has been reported, due to its effort to dispose of the

* Some cases have been reported, however, in which, after removal of the exciting cause, no characteristic signs and symptoms can be detected even after intensive study.—EDITOR'S NOTE.

excess of bilirubin brought to it by the blood. In patients being splenectomized the liver has usually appeared normal. In a recent communication, however, Pemberton[8] reports that in 118 splenectomies, evidence suggesting secondary involvement of the liver was observed in 55 cases. In 7 of these the appearances of cirrhosis were noted by the surgeon and in 6 others ascites was found. In the remaining 32 the liver was described as enlarged, congested and hard.

2. Special interest has always attached to *the spleen* in this disease; but again there seems to be almost universal agreement that this organ, like the liver, has not undergone any pathognomonic change. Abundant material has been available for investigation since splenectomy became a generally adopted method of treatment. At The Mayo Clinic, for example, McCarty[9] reporting 50 spleens says that the excessive size is mainly due to overfilling with blood; and that there is no particular alteration of the structure of the spleen in any of its parts. This agrees with Meulengracht's opinion based upon the examination of 12 spleens and also with that of Gänsslen on 10 spleens removed at operation. On gross examination the spleen is always enlarged, 4 to 10 times its normal size, weighing in adults 800 to 2000 gm. instead of the normal 150 to 250 gm. The surface is usually smooth and normal in appearance, and does not show the pronounced perisplenitis or thickening of the capsule seen at times in other diseases, such as Banti's. On the cut surface the predominant appearance is the excessive richness in blood. The consistence is somewhat softer than the normal, due to the disproportion between the blood and connective tissue. Microscopically, there is an enormous increase of blood in the interstices of the pulp with relative emptiness of the sinuses. Some pathologists find both pulp and sinuses engorged. This picture has been accepted generally and is interpreted to mean a hyperactivity of the spleen, due to an increase in its hemolytic function. As Sjövall and Ivarsson[10] have expressed it, the appearance of the spleen in chronic hereditary hemolytic jaundice in no way differs qualitatively from a spleen reacting normally; the examination showing simply an organ which, itself of normal structure and well capable of function, is forced to overwork.

3. *The bone marrow* has recently been recognized as intimately connected with the changes found in the blood and responsible for much of the clinical picture presented. Up to 1922 there had been few references in literature to the condition of the bone-marrow. Guizetti[11] in 1912 had reported a case in which he found signs in this structure of an enormous hyperactivity, with the fatty marrow crowded and thinned by the red erythroblastic marrow. Sisto[12] in 1917 had described exactly the same picture. Meulengracht's conclusion that the bone marrow in this disease presents a typical condition of hyperfunction has since been verified by other

investigators. Friedman,[13] reporting in 1928 the results of autopsy in a typical case of a girl, aged 4½, who had died shortly after splenectomy, found the bone marrow markedly hyperplastic and deep red, with no fatty marrow visible in femur, sternum, ribs or skull. Wade and Steigrad[14] reported similar autopsy findings in 1928 in a case observed in Sydney. Neuburger[15] in 1931 described bone marrow obtained by sternal puncture in studying the effects of liver extract upon chronic hereditary hemolytic jaundice, which showed the same changes. In tibial trephines of 4 adult patients Escudero[16] found hyperactivity of the bone marrow, even in the diaphysis, which normally is inactive in the adult. Erythroblasts were always in excess, but there were also many myeloblasts, lymphocytes, and neutrophilic granulocytes. Thus from all the evidence at hand it seems fair to conclude that the bone marrow is simply overworked, but condemned by the hereditary factor to put out fragile erythrocytes.

4. *Other organs* show no pathologic changes of importance. Pigmentation has been reported in various viscera, liver, spleen, lymph nodes, bone marrow, and so on. Minkowski stated in his original report that siderosis of the kidneys was one of the essential features of the disease, but this condition has since been found to be inconstant, and of no special significance. In fact, all changes except those in the spleen and bone marrow are of secondary consequence; and no organ by its abnormal structure supplies any direct proof as to the real underlying pathogenesis of the condition.

Clinical History. The symptoms vary greatly in two respects; first, as regards their onset and, second, their severity. (*a*) The disease may show itself: (1) at birth as icterus neonatorum and be definitely congenital; or (2) during the first, second or third year of life, or at any time during the first decade; (3) or no definite evidence of ill-health sufficient to attract attention may be noted until the second decade; (4) or it may even be not until the third decade or later that abnormalities are presented of such importance as to lead to a thorough medical examination and a diagnosis. When the onset is late, the previous history may contain no incidents to suggest that the disease was really congenital; though careful investigation by physical examination and laboratory tests might have shown characteristic abnormalities even during those earlier years, at a time when there was no complaint and the patient was not aware of anything unusual. These are the latent cases ("formes frustes"). When manifestations do ultimately arise to make the diagnosis known, it is not uncommon to assume that the disease has just appeared and has been acquired.

(*b*) The individual symptoms may differ much in the degree of their intensity. They may be so slight as to be almost unnoticeable or so severe as to threaten life. Even in the same patient the condition is subject to such variations at different times. With slight

attacks the symptoms may be so little pronounced that they cause no inconvenience and attract little or no attention (see Gilbert's "Cholémie familiale"). Neither the patient nor his friends observe that he is either pale or yellow. On the other hand there are some who are always anemic and restricted in their normal activities. This is well exemplified by the history in Case 2. They complain particularly of weariness and weakness, of lack of initiative and of shortness of breath and pounding of the heart on exertion. Their color is also always sallow and may be frankly that of jaundice; though this is usually moderate in degree and only rarely reaches the deep mahogany brown tint seen at times in jaundice from other causes. Sometimes there is complaint of abdominal pain but only in connection with exacerbations of the illness or with some complication such as gall stones.

The duration of life in these patients is remarkably little affected by the disease. Case 1 is a witness to this fact (she had reached 67 in spite of chronic jaundice and enlarged spleen for years) that many have attained advanced age. The cause of death even then is frequently some intercurrent ailment. When death does result directly from the disease, it is usually due to progressive anemia. While in the majority of patients the course of the disease is comparatively uneventful without tendency to spontaneous recovery, in others it is interrupted by exacerbations that may prove severe. After a longer or shorter interval, during which the patient feels fairly well, there comes rather suddenly, even in the course of 1 day, an intensification of all the symptoms. Weakness, pallor and jaundice are all more decided and abdominal pain becomes a prominent feature, felt usually in the region of the spleen, but sometimes over the liver or in the epigastrium. Slight fever, nausea and vomiting are not unusual. Physical examination at these times shows the splenic tumor considerably increased in size, laboratory examination discloses a marked decrease in the hemoglobin and the number of red cells from previous observations. Such exacerbations are known clinically as "crises" ("crises de deglobulization," or "crises hemolytiques"). They have been described by observers in a number of different countries and constitute in some cases a characteristic feature of the disease. Sometimes one of these attacks has been the first definite manifestation that has led to the careful investigation required for a diagnosis. They are explained as the result of destruction in the spleen of a larger amount of red blood corpuscles than ordinarily takes place, occurring more rapidly than the hyperfunctioning bone marrow can replace the loss. These crises are uncommon. They may occur, however, in some cases every few months or few weeks, last for a few days, then again be followed by gradual improvement and return to a state of comparative health, such as existed before the exacerbation. They are brought on

apparently by emotional disturbances such as fear, grief, worry, as well as by bodily overexertion or by any acute infection. In women, they may be induced by menstruation or by pregnancy.

It is generally accepted that signs of bile toxemia, such as are common in obstructive jaundice, are not observed in this disease. There is no itching, bradycardia, or tendency to hemorrhages. This is explained by the fact that the blood contains no excess of bile salts but only of bile pigment. This type of jaundice, known as "dissociated," is always found when hemolysis is the cause, no matter how it is produced.

Complications. Several different consequences of the disease may attract more attention than the underlying condition itself. (1) The latent or comparatively insignificant anemia that usually characterizes the course may become so extreme that it dominates the picture and produces symptoms resembling those of so-called pernicious anemia. But in these cases there is usually no achylia, the splenic tumor is much larger, and there is never any glossitis. These points in the examination are as a rule decisive when taken in connection with the condition of the blood and the previous history of the patient. Details in the differentiation will be given later in the discussion of diagnosis.

2. In a large proportion of the cases coming to operation for splenectomy, in as high as 68 per cent according to Pemberton,[8] conclusive evidence is found of disease of the gall bladder, though such symptoms are much less often produced. In a few instances, definite attacks of biliary colic with true obstructive jaundice alternate with hemolytic crises, but patients themselves learn to distinguish between the two.

3. Eppinger[17] has called attention to complicating ulcers on the foot, that healed with great difficulty or not at all by ordinary measures. These were found on the inner or outer side of the foot, in the malleolar region. They had slight secretion, did not form granulations in response to treatment, bled easily and caused pain sufficiently severe to interfere with the patient's work. Women found them particularly painful at the time of menstruation. Such ulcers, which might exist for years, either occurred in association with other characteristic features; or might be found without any other symptoms or signs than the blood picture. In two typical families, Eppinger was able to demonstrate a family occurrence of such non-healing foot ulcers; either in combination with jaundice and splenomegaly, or only with increased fragility of red blood corpuscles and evidence of hemolysis. After every other means of therapy had failed, Eppinger twice observed a rapid healing of these ulcers after splenectomy, even before other manifestations of the disease had disappeared. Seelig and Jaffe[18] have reported another similar case; but Gänsslen[19] had previously reported this complica-

tion several times and others had done likewise. One of Gänsslen's cases of ulcer after unavailing treatment for 9 months by routine methods, healed in 8 days after splenectomy.

4. Changes in the skull and the long bones have been described by a number of different observers as occurring especially in children. Friedman[13] reported in 1928 4 children, all under 13, studied Roentgenologically. They showed moderately large skulls with thickened, frontal and parietal bones, the tables thin, the diploe widened and mottled with minute rarefied areas. The bones of forearms and hands presented a pseudoatrophic appearance, with numerous small areas of rarefaction and striation, so that the structure appeared "moth-eaten." He regards these osseous changes as definitely pathognomonic.

Wade and Steigrad,[14] also in 1928, described similar changes in 3 children in Sydney. All of them presented the typical findings of chronic hemolytic jaundice, but in addition a prominence of the frontal and parietal bosses, with furrows corresponding to the sutures, giving the front part of the head a "hot cross bun" effect. Sear,[20] who described the Roentgen ray appearances, says that the frontal and parietal bones which were the most involved showed great thickening, gradually decreasing as the sutures were approached. The most peculiar feature was a vertical striation, remarkably even and uniform, not seen in rickets or any other disease. Sear believes that the three cardinal features of chronic hereditary hemolytic jaundice are anemia, splenomegaly and the changes in the osseous system.

Again it was Gänsslen[21] who deserves priority in the recognition of these osseous changes, having called attention to them in 1922. Gänsslen says he saw this abnormality, to which he gave the name "Turmschädel" (tower skull), in almost half of his cases in children.

Physical Examination. The characteristic signs of this disease are first the patient's color, due partly to anemia and partly to jaundice; and second the enlarged spleen. The liver is rarely increased in size sufficiently to attract attention. If it is decidedly enlarged, the correctness of the diagnosis should be questioned, or the presence of some complication suspected.

(*a*) The patient's pallor is so slight in some cases as to escape observation; or so extreme in others as to attract immediate attention. Even in the same patient this anemic appearance varies with a fairly normal color for weeks or months, and then a persistent whiteness of the skin again is predominant. This pallor is always more pronounced during and following a crisis. The jaundice likewise is usually slight, more a sallowness than a true icterus. It may not be noticeable at all on inspection, even when the blood serum shows an abnormal amount of bilirubin. But in other patients, icterus may be conspicuous and as deep as that due to obstruction. This peculiarity prompted long ago Chauffard's dictum that such

patients are "more icteric than sick." In all patients the intensity of the discoloration is changeable, varying at different periods like the anemia. There is no constant parallelism, however, between the two. In some instances they agree, but on the other hand with deep pigmentation of the skin only slight anemia may be found; and with anemia of high degree very little jaundice may be evident. This disparity is explained by the fact that while hemolysis is responsible in this disease for both the anemia and the icterus, the visible degree of either depends upon the functional capacity at the time of the bone marrow and the liver.

(*b*) Enlargement of the spleen is a constant sign, though the degree varies greatly. Undoubtedly the increase in size may be so moderate that its demonstration clinically by any method is difficult and indefinite. A few cases have been reported where the spleen did not seem to be enlarged but these apparent deviations seem to have been due either to faulty observation or incorrect diagnosis. On the other hand, the splenic enlargement may be extreme, so that the organ occupies the entire left side of the abdomen, as low as the spine of the ilium and sometimes passes the middle line. Its size varies in the individual patient with the severity of the condition at the time, fluctuating with remissions and exacerbations of the disease. During a crisis the spleen is always larger, firmer and more tender; after the crisis is over, it rapidly subsides.

Laboratory Examinations. 1. *The blood* examination is absolutely essential as it is evidence upon which diagnosis of the disease depends. (*a*) *Number of red cells.* This may be very low, or it may be normal or in rare cases even above normal. As a rule the hemoglobin is found between 60 and 80 per cent, and the red cells between 3 and 4 million. Usually, therefore, the anemia is moderate. Rarely do the figures fall below those mentioned except during crises; that this may occur sometimes even without crisis is shown by the count in Cases 1 and 3. In quiet periods of the disease the hemoglobin percentage may be quite normal, also the erythrocyte count. Reduction in hemoglobin usually is parallel with decrease in the number of red cells, so that the color index remains approximately normal.

(*b*) *Size of Red Cells.* In stained smears of the blood, the red cells vary much in size (anisocytosis). But even more important, there is a predominance of small cells ranging from 6 to 7 microns (instead of the normal average of 7.5 microns of dried spread). As Gänsslen says: "in the majority of cases microcytosis rules the picture but all the cells are not affected in this way." Furthermore not only the size but the form of these cells is unusual, because in spite of the unnaturally small diameter they have a proportionately large volume, having become more spherical than usual. Actually, then, these erythrocytes are of normal size, as their volume is normal; and the term microcytosis is not proper here. However, as cells of

small diameter are universally designated microcytes, the term has been retained.

By some observers these peculiarities in the size and form of the red cells, so essentially different from normal have been considered one of the distinguishing inherited characteristics; but there are several objections to this theory. First, microcytosis in a few cases has been reported as entirely absent, even though the diagnosis was indubitable. Second, microcytosis with relative increase in volume of the cells is not peculiar to this disease but has been observed in several other anemias. And third, patients have been reported in whom after splenectomy all microcytosis has ultimately disappeared. It seems probable, therefore, that the explanation for microcytosis in this disease is simply that these small round cells represent the subnormal response of an overstimulated bone marrow whatever the cause. In the rare exceptions which have been reported without microcytes and in those where they disappear after splenectomy, erythropoiesis is evidently not so heavily taxed, as Escudero's bone-marrow studies show; and consequently microcytosis is little or not at all evident.

(*c*) *Reticulocytes.* Another peculiar feature is the presence in the blood smear of a greater or less number of red cells with granular filamentous structure brought out by vital staining. These reticulocytes (Krumbhaar[22]) are regarded as immature red cells sent prematurely by the bone marrow into the circulation to replace those destroyed by hemolysis. They occur in normal blood but never exceeding 1 per cent; while in chronic hereditary hemolytic jaundice they are frequently increased in number to 5 or 6 per cent, or to 20 or 30 per cent or even more in exceptional cases. For instance Baty[23] has recently reported a patient where the reticulocytes constituted 92 per cent of the red cells over a long period of observation; and Reynolds[24] another one where there were 95 per cent. On the other hand, the number may not rise above 1 per cent even when other characteristic features make the diagnosis certain, as was observed in Cases 1, 2 and 3 and also 4 reported later on in this review. It was Chauffard who first called attention to them in this disease though, like microcytes, they are found increased in other anemias. Their number may increase in the same patient from time to time, coincident with "crises;" falling again to a lower figure during the remissions, even below 1 per cent, as in normal blood.

(*d*) *Increased Fragility of the Red Cells.* The most characteristic change of all those found in the blood in this disease is decreased resistance of the red blood cells to osmosis; or as it is better known, increased fragility. This is likewise one of the discoveries made by Chauffard but long since generally confirmed by other observers. It is an almost constant manifestation in chronic hereditary hemolytic jaundice, and is practically pathognomonic of it. It has been reported in other diseases of the blood, such as pernicious anemia,

posthemorrhagic anemias and various forms of leukemia, which usually show decreased fragility, but never to the same degree as in this condition. Its diagnostic value has been established beyond question and it seems to be the one essential feature upon which diagnosis depends. This peculiarity of increased fragility is not restricted to cells below the average size; on the contrary, an excessive number of microcytes in the blood tends to increase the resistance to osmosis and to make the figures for hemolysis more nearly normal. This is explained by Gänsslen[25] as due to the fact that as microcytes are more globular than normal red cells, and really have greater volume than the usual disklike erythrocytes, they can offer more resistance to disintegration by water. Furthermore, when reticulocytes, which are more resistant, are present in large numbers, the fragility of the red cells may be found within normal limits (see Reynold's case already cited). The cause of the increased fragility is not absolutely settled. By most authorities it is accepted as the congenital defect inherited by the individual that constitutes the essential feature of the disease. By some it is interpreted as just another regeneration symptom, like microcytosis and reticulocytosis, the result of forced action by the bone marrow. Still others have attempted to prove that it is the result of toxic or hemolytic substances in the circulation, arising from some unknown source. It is significant that no cases have been reported where this feature became entirely normal after splenectomy, even though it became more nearly normal; but this improvement effected by removal of the spleen is certainly highly suggestive.

(*e*) *The White Blood Corpuscles* as a rule are normal in number, any tendency to variance being usually on the side of excess. The normal proportions of the different varieties of white cells is also usually maintained. During the crisis, counts of 20,000, 30,000 or even higher may be found in exceptional cases. This increase is mainly due to polymorphonuclears, but myelocytes may also be found in moderate numbers. Immature red cells, particularly normoblasts, are likewise to be seen in the blood smears following a crisis, and the entire picture is that of overactivity and hasty formation. According to Gänsslen the blood platelets are usually normal in number or increased, rarely decreased, but no great number of observations regarding the platelets has been met with in the literature.

(*f*) *Blood Serum.* Bilirubin is present in abnormal amounts. The jaundice, being due to excessive disintegration of red blood cells, is properly designated hemolytic. When bilirubin pigment, carried to the liver for removal from the body, exceeds the amount that the hepatic cells can excrete, some of it is carried back to the general circulation without entering the bile at all; the rest escaping in the usual way with the bile into the intestine. This type of jaundice has been given the name "dissociated," because the blood

serum contains bile pigment in excess but not bile salts; this separation being the consequence of the failure of the hepatic cells to form these latter ingredients. So far as known, bile salts do not exist normally in the blood at all, but are constructed in the polygonal cells of the liver and acquired there by the bile as one of its ingredients. Unless the bile is subsequently obstructed and reabsorbed, bile salts never are found in the blood. Tests of blood serum by the method of Meulengracht usually show a lower icterus index in chronic hereditary hemolytic jaundice than in obstructive jaundice. Assuming the normal index as 3 to 5, the figure in this disease rarely runs above 30, except after a crisis, when it may temporarily be found much higher, but on the other hand, it never is within normal limits, even when clinically no jaundice is present. By the van den Bergh test, the direct reaction is negative, but the indirect may run as high as 5 or 6 units, the normal being 0.5 of one unit.

The Wassermann reaction is of course negative except in the presence of a complicating syphilis. Attempts have been made by some observers to claim that the disease is itself a manifestation of syphilis; but the great majority of those reporting cases have found the blood serum negative and nothing in the history or the physical findings to justify this theory.

2. *The Urine.* In obstructive jaundice darkening of the urine by bile is a characteristic feature. But in this variety of jaundice either the urine is of normal color, or even if dark, bile pigment is absent. In Minkowski's original description, this peculiarity so attracted his attention that he called the disease "Acholuric Jaundice." Abnormal amounts of urobilin may be found, and even bilirubin, during "crises." When the amount of bilirubin is large, the urobilin is likewise.

3. *The Feces.* Decrease or absence of pigment in the stools is a feature of obstructive jaundice, so that they are characteristically light yellow or clay colored. In this variety of jaundice, however, just the opposite is seen. Abundance of urobilin in the intestine keeps the feces their usual color or even darker than usual. If at any time in the course of chronic hereditary hemolytic jaundice this picture changes, with bile in the urine and none in the stools, it indicates a complicating obstructive jaundice, usually due to a gallstone blocking the common duct. This, however, is exceptional and should cast no doubt on the original diagnosis.

Diagnosis. In typical cases, recognition of the disease should be easy. The common history of jaundice over long periods, varying in amount or replaced by periods of pallor, alternates with periods when the color is fairly normal. Varying degrees of weakness and lack of energy may be replaced by a sudden intensification of all the symptoms and the addition of abdominal pain. The enlargement of the spleen is important, but even this may be so moderate in some cases as to be indefinite. The diagnosis really rests on

examination of the blood. The characteristic abnormalities are not only a secondary anemia of varying degree, but anisocytosis, microcytosis, reticulocytosis and especially decreased resistance of the red blood cells to osmosis. The amount of bilirubin in the serum is always above normal. The urine contains no bile except in crises but is darkened by urobilin. The stools are not acholic but even darker than normal. No other disease gives this picture though others may resemble it in some details. The key to final decision always depends upon the blood findings.

The presence of microcytosis with relatively large volume of the red blood cells is of equal value in suggesting the disease with the fragility test when jaundice is present. This is clearly demonstrated by the fact that in 6 of the 8 cases here reported the first positive suggestion as to the true diagnosis was derived from the finding of marked microcytosis of the erythrocytes.

As methods of determining the diameter of erythrocytes have been adequately discussed by Haden,[26] they need be only briefly mentioned here in order to point out that the procedure is simple. There are three such methods generally recognized. The diffraction method, suggested by Pijper,[27] gives only the average mean diameter of the red cells; the same principle has been used by Eve[28] in constructing the halometer. The practicability of this instrument has already been reported upon.[25,28,29] The other two methods involve the actual measurement of the diameters of a large number of cells, usually 200. The micrometric method is in general use for this purpose. In the projection method the image of the cell is directly measured[31] or the outline is drawn and subsequently measured.[32]

Normal values for erythrocyte diameters have been fairly well established.[33] The normal average of dried cells is between 7.2 microns and 7.7, with perhaps 7.5 microns as the figure most commonly accepted in this country. Price-Jones has constructed a curve to show diagramatically the incidence of each size of cell. He recognizes normal curves, curves showing a macrocytosis with a "shift to the right" and curves showing microcytosis, with a "shift to the left" (Fig. 1). The normal is taken from Wyckoff[34] and is based upon a study of a hundred individuals. The curve with the peak to the right is from a case of pernicious anemia and is quite typical. The curve with the peak to the left is from our own Case 1.

Red blood cell volume determinations are readily carried out from a count of the number of erythrocytes and hematocrit readings showing the per cent of red cells in a given volume of blood. This may be expressed in terms of volume index as described by Haden[35] or in terms of individual cell volume. The average normal cell volume is about 85 cubic microns and usually lies between 75 and 95. A macrocyte is larger than 95 cubic microns and a microcyte is smaller than 75. As has been explained, the volume of the microcyte in chronic hereditary hemolytic jaundice is nearer normal than

the diameter, so that red cell volume determination alone is of little diagnostic value.

Halometer readings and Price-Jones measurements have been carried out on dry blood films on all but 2 of the cases herewith reported and the results are presented in Table 1. In each instance the average red cell diameter was less than 7 microns and in Case 3 was only 5.93 microns, the smallest we have observed. While many normal-sized cells are found, the number of small cells observed is in striking contrast to the usual blood picture. Figure 2 shows the so-called "shift to the left" of the peak of the curve that characterizes this disease.

Although such a shift to the left is characteristic of microcytosis, it must not be forgotten that it may also occur in other conditions and is therefore not diagnostic of chronic hereditary hemolytic jaundice by itself; although in this disease its presence is practically constant, except after splenectomy. As a rule, however, all other diseases associated with microcytosis may be easily differentiated. Chronic long-standing infections, nephritis, chronic hemorrhage, simple achlorhydric anemia, an occasional case of erythremia (Osler-Vaquez disease), possibly some of the anemias of cancer, and acidosis are all associated at times with microcytosis, but the clinical aspects of these conditions are quite different. Out of a total of 793 miscellaneous cases studied with the halometer, only 24 have been found with average red cell diameter in the 6 micron range; and of these 6 (25 per cent), proved to be chronic hereditary hemolytic jaundice.

Furthermore, *the occurrence of pronounced microcytosis in the presence of jaundice, whether clinical or latent, may be considered almost diagnostic of chronic hereditary hemolytic jaundice.* Warburg[36] has pointed out that most types of jaundice are often associated with the presence of large red cells; and it is now recognized also that the degree of this macrocytosis is proportionate to the anemia that coexists.[37] In all other forms of jaundice except that now under consideration, the erythrocytes in our experience are normal or above normal in size. In 70 patients observed with clinical jaundice or with definitely increased serum bilirubin (exclusive of pernicious anemia where the tendency to macrocytosis is well recognized), none showed microcytosis except the group of cases herewith reported, and many showed a definite macrocytosis. General recognition of this fact should lead to a more prompt diagnosis of this infrequent but not altogether rare disorder.

The macrocytosis of pernicious anemia should be emphasized as the latter is often mistaken for the condition under discussion. Such an error was made repeatedly in Case 2, and also in Case 6 before it came under our observation. Although there are several clinical and hematologic features that may be the same, the difference in red cell size and fragility in the two should prevent con-

fusion. This is well illustrated by the Price-Jones curves in Fig. 1. Erythroblastosis also may offer difficulties in differential diagnosis.[38] However, a study of the blood film shows extreme poikilocytosis in this rare disease; cell measurements in the 2 cases that have come under our observation show average diameters of 7.4 and 7.5 microns, and the form of the Price-Jones curve is close to normal.

TABLE 1.—ERYTHROCYTE DIAMETERS OF 200 CELLS IN 6 CASES OF CHRONIC HEREDITARY HEMOLYTIC JAUNDICE. COMPARISON WITH AVERAGES IN A NORMAL CASE.

R.B.C. diameter in microns.	Number of red blood cells.						
	Case 1.	Case 2.	Case 3.	Case 6.	Case 7.	Case 8.	Normal.
4.4	3	2	5	1	4	..	0
5.0	18	15	32	2	17	3	0
5.6	43	36	53	6	37	29	3
6.3	78	89	85	56	74	97	17
6.9	42	40	18	88	39	55	30
7.5	11	14	7	41	22	11	98
8.1	4	2	0	5	6	4	32
8.8	1	2	0	1	1	1	15
9.4	0	0	0	0	0	0	3
10.0	0	0	0	0	0	0	2
Average diameter	6.2μ	6.3μ	5.9μ	6.8μ	6.4μ	6.3μ	7.5μ
Halometer reading of average diameter	6.5μ	6.3μ	6.3μ	6.7μ	6.3μ	6.6μ	7.5μ

Treatment. Treatment with iron, arsenic and other blood building drugs never has accomplished more than temporary improvement of the anemia. Radiation over the spleen, long continued, has been without effect. Transfusion produces only temporary improvement but is a desirable preparation for splenectomy. It stands to reason that no benefit can be expected from removal of the gall bladder; yet this has frequently been done. In general, no treatment ever proved of value except removal of the spleen.

Splenectomy has now become the therapeutic measure generally accepted. It was first performed for this disease in 1907 upon a case reported by Vaquez and Giroux.[39] As it unfortunately resulted fatally, no further resort to the procedure was made until 1911, when Micheli[40] reported a successful splenectomy with immediate cure. This soon stimulated other successful operations until today, after 20 years of trial, it has become the accepted method of treatment, once the diagnosis is made. Reports from many surgeons, in different parts of the world, are favorable as regards the immediate outcome. For instance, Beckman and Jäderholm[41] have recently collected the results of 18 splenectomies performed in Sweden by 6 different operators, with no history of a primary mortality. Herfarth[42] in 1926 collected 176 splenectomies with only 6 deaths following operation. In 1931 Pemberton[8] reported 118 splenectomies performed between 1911 and 1931 at The Mayo Clinic, with only 4 deaths, an operative mortality of 3.4 per cent. Certainly, therefore, from the standpoint of possible fatality, the operation is not to be shunned as too dangerous.

As regards clinical results, all accounts are enthusiastic. Meulengracht's[6] 12 patients who had their spleen removed attained a clinically perfect cure; Gänsslen's 25 cases had all symptoms disappear shortly after splenectomy. Pemberton reports that evidences of benefit are apparent in 5 to 8 days after operation. Jaundice that has persisted for years fades and disappears in from 2 to 3 weeks. There is also rapid and progressive improvement in the anemia and a clinical restoration to health.

From the laboratory standpoint, following removal of the spleen, bilirubinemia promptly approaches the normal limits. The red cell count likewise comes back to approximately the figures found in health and so does the hemoglobin percentage. But all authorities agree that anisocytosis does not always disappear, even though it becomes less marked; that microcytes continue to be demonstrable in most cases; that reticulocytes usually but not always return to their normal percentage; and that abnormal fragility of the red corpuscles, though lessened, never entirely disappears. Escudero[16] has shown by biopsy on bone marrow before and 4 months after splenectomy that the tibial medulla returns to a state of functional repose after its previous hyperactivity. In other words, though the patient is restored to health after operation, the characteristic features of the blood picture, though greatly improved, do not altogether disappear.

The spleen is not the cause of the disease, but as has been said by Hellström,[43] it is only the organ that transforms into a disease what was previously only an abnormality. Splenectomy cannot remove this inherited abnormality, the faulty formation of red blood corpuscles, and this persists subsequently, as proved by blood examinations. If the spleen is removed, red cells of inferior quality have lost their destroyer. The bone marrow can easily perform the task of regeneration. Furthermore, the liberated bilirubin reaches the liver in smaller amounts so that it does not overwhelm the hepatic cells.

How well can the body get along without the spleen? A number of functions have been attributed to it (Krumbhaar[44]) and, in particular, its activity against infections (both humoral and by removing bacteria and toxins from the blood). But no disturbances of any practical importance have been observed after its removal, presumably because other members of the reticulo-endothelial system not only share in its functions but soon compensate for its absence. However, there is one interesting observation to be noted (Beckman and Jäderholm[41]) Of the 18 Swedish patients whose spleen had been removed for this disease, 7 subsequently developed tuberculosis. They felt that even though the disease itself might before operation have decreased the patient's resistance to infection, nevertheless the elimination of the protective function of the spleen by splenectomy caused the tuberculous infection to take

on a more active course. Fortunately this unusual postoperative experience is unique in the literature.

The brilliant results achieved by liver extract in pernicious anemia naturally suggested the same treatment for chronic hemolytic jaundice, but most accounts of its use have been unfavorable. In Neuburger's[15] 2 cases no effect upon the anemia was observed, nor was hemolysis arrested or jaundice decreased. Also in Jedlicka and Varadi's[45] 3 cases no effect at all was noted, either subjective or objective; in fact, in one the jaundice became more intense, and the spleen markedly increased in size. On the other hand, Ordway and Gorham[46] report a case greatly improved, at least temporarily, by the use of "a potent liver extract," one vial t. i. d., for 5 months. In cases where splenectomy is refused or seems for some reason contraindicated, liver therapy deserves further trial.

Apparently but few cases have been observed on the Pacific Coast. They must be rare, for the 2 following are the only ones seen in the clinical service at Stanford Hospital as far back as adequate histories are available for review.

CASE 4.—A woman, aged 34, entered the obstetrical service at Stanford Hospital in January, 1926, for delivery. She was decidedly jaundiced and said she had been so since childhood, in fact since 3 days old. There had been no intercurrent illnesses except measles, mumps and whooping cough in childhood. Twelve years earlier she had submitted to an exploratory operation to discover whether a diseased gall bladder was the cause of her jaundice, but was told no abnormality of that organ was found. She had had 5 children and was now approaching the end of her 6th pregnancy. She said that her yellow color was always accentuated during her pregnancies but even between them it never disappeared. In spite of her jaundice, she had always been strong and healthy and had no complaint to make. On physical examination, besides the obvious jaundice and the uterine enlargement, very little was found. The heart and lungs were normal and the liver and spleen were not palpably enlarged. Laboratory examinations showed no anemia, the hemoglobin being 89 per cent, the red cells 5,055,000, with white cells 8925 per c.mm. There were no marked abnormalities in the smear and the differential white count was polymorphonuclears 68, lymphocytes 29, transitionals 3 per cent. The reticulocytes did not exceed 1 per cent. Fragility of red cells, however, was increased and they began to hemolyze at 0.48 while a normal control with the same solutions did not begin until 0.44. The direct van den Bergh reaction was negative but the indirect markedly positive. The icteric index was 25. The urine was normal except for the presence of urobilin in excess. Althogether this case, though well compensated, fitted no other diagnosis except chronic hemolytic jaundice. The patient went through labor without any complication and left the hospital well. In March, 1927, she entered another hospital in San Francisco, apparently in a crisis, for the history says she was deeply jaundiced, was vomiting, and had pain in the right back and great tenderness over the right upper quadrant. A diagnosis was made of stone in the common duct although Roentgen ray films after the dye, given once by mouth and once by intravenous injection, failed to show any stone and yet gave good "visualization" of the gall bladder; which does not occur when jaundice is of the obstructive type. At operation the gall bladder was found normal but removed. No stones were discovered, although the ducts were probed in the effort to reveal them. No special blood studies were made, and the

true diagnosis was apparently not suspected. A few days following operation the patient died. No autopsy was done.

Case 5.—A woman, aged 43, entered the clinic ward of Stanford Hospital in December, 1931, complaining of weakness and persistent jaundice, with attacks of vomiting. She had no pain of any kind and had not experienced any during her illness. She had never heard of any such condition as her own in her parents or in any of her 6 brothers and 4 sisters. The only previous illness she could recall was a swelling of the neck first noted in 1911, with exophthalmos and extreme nervousness. She says this was relieved by a few electrical treatments at the time, and the swelling subsided after several months. In 1926 she had a choking sensation, with marked edema of legs, arms and face. This was cured by taking thyroid extract off and on for the next 2 years. Her present sense of weakness and progressively deepening jaundice began in April, 1931, and her vomiting attacks in August, 1931. The most striking feature about this patient on physical examination was her color. She presented a remarkable shade of yellowish-brown, uniformly distributed, suggesting that of a negress. No abnormality was noted otherwise except that both the liver and the spleen were palpable about two fingers' breadth below the costal margin. The thyroid gland was certainly not enlarged. The blood count showed a pronounced anemia; hemoglobin 39 per cent; red cells only 2,160,000 per c.mm. The white cells were 7700 (polymorphonuclears 80, lymphocytes 11, large monocytes 5, eosinophils 1, basophils 1 per cent and 1 myelocyte noted). There was marked anisocytosis and polychromasia and 43.6 per cent of reticulocytes. The red blood corpuscles were fragile, hemolysis beginning at 0.46, complete at 0.34, while in the control it began at 0.38 and was complete at 0.21. The direct van den Bergh test was negative, while the indirect measured 3.5 units. The icterus index was 21 to 23. There was no bile in the urine but excess of urobilin. The feces were dark brown. The Wassermann reaction was negative. Gastric analysis showed no free hydrochloric acid after histamin, but Roentgen ray examination of the gastro-intestinal tract failed to reveal any defect that might be attributed to neoplasm, and no gall stones were seen in the films. The basal metabolic rate was +4. This patient thus presented a characteristic picture of acquired hemolytic jaundice. In spite of transfusion the blood did not improve, therefore splenectomy did not seem justifiable. The patient returned to her home in the country and died there on December 17, 1931, apparently from progressive anemia. No autopsy was done.

Case 6.—Observed in private practice, is particularly interesting because of the problem presented in differential diagnosis. A man, aged 52, seen in April, 1931, had a persistent anemia, previously diagnosed as pernicious. His family history, carefully investigated, revealed no known anemia, jaundice or splenomegaly in any other member among his grandparents, parents or brothers and sisters. Both anemia and jaundice appeared 20 months before he came under our observation, a diagnosis of pernicious anemia was made and he was given liver, liver extract and ventriculin more or less continuously for 18 months. However, he never responded well and 4 blood transfusions had been required. At one time he had been told that his hemoglobin was as low as 20 per cent and his red cells less than one million. He had consulted several different physicians, one of whom suggested splenectomy, but all others were opposed to this. At the time we saw him first, he was somewhat better, but naturally anxious to know the true nature of his condition and whether liver therapy ought to be continued. Physical examination showed the patient well developed and nourished but with definite pallor and a lemon-yellow tint in his skin. The tongue was normal. Except that the spleen was readily palpable just below the left costal margin, no evidence was found of any visceral disease. Labora-

tory examinations showed nothing unusual in the urine and stools. The blood Wassermann and Kolmer tests were negative. The icterus index was 15. The direct van den Bergh test was negative; the indirect 2.5 units. Blood examination gave a hemoglobin percentage of 75, red cells 3,560,000, white cells 8000 (60 per cent polymorphonuclears, 37 lymphocytes, 2 transitionals and 1 eosinophil with marked anisocytosis and polychromatophilia). There were 5 per cent of reticulocytes. The most striking feature was the preponderance of small red cells with an average diameter of 6.7 microns. By the fragility test, hemolysis began at 0.5 per cent and was complete at 0.42. After an alcoholic test meal, no free hydrochloric acid was found and the total acidity was only 6; but after an injection of 0.5 mg. of histamin, the total acidity was 62 and the free hydrochloric acid 51. In this case measurement of the erythrocytes afforded information of the utmost importance. The combination of anemia, jaundice and splenomegaly, when definite microcytosis was added, made the diagnosis of pernicious anemia seem improbable. Furthermore, the free hydrochloric acid in stomach contents, the increase in reticulocytes, the definite loss of resistance to osmosis by the red cells and finally a Price-Jones curve showing a positive shift to the left, all combined to make practically certain the diagnosis of chronic hemolytic jaundice. Splenectomy was advised but was refused. The subsequent course of the patient is unknown.

Finally, the 2 following cases cannot be positively set down as chronic hereditary hemolytic jaundice because the data are incomplete, but what was found strongly suggests this diagnosis.

Case 7.—J. L. M., a 42-year-old married white American was seen in August, 1932, complaining of indigestion. The family history of his grandparents was unknown, but there was nothing remarkable in that of his parents or his brothers and sisters. The past history was essentially negative except for gonorrhea at 20. Alcohol was used sparingly. For 15 years he had had recurrent attacks of right upper quadrant distress with indigestion and occasional vomiting. He believed he had been more or less yellow during this time. He had had no real colic, and had not been noticeably pale. He was well developed but undernourished. His skin was a yellow tan color, but not definitely jaundiced. The sclerae were slightly icteric. The rest of the examination revealed nothing unusual except questionable tenderness at the right costal margin. The spleen was not felt. His urine, feces, sputum and blood Wassermann tests were negative. The red blood count was 4,930,000; hemoglobin 90 per cent. There were 8000 white blood cells, with a normal differential count. The icteric index was 15, and later 13. The direct van den Bergh was negative, the indirect was 1.3 units, later 1.8 units. A gastric test meal showed a free acid of 71 and total acidity of 81 after an alcohol meal. The basal metabolic rate was −10. Roentgen rays of the sinuses, chest and gastro-intestinal tract were negative. The gall bladder failed to visualize by oral or by intravenous tetraiodophenolphthalein. A Price-Jones curve of erythrocyte size showed an average diameter 6.42 microns, but the patient returned to his home in Montana before further special studies of his blood could be made. A diagnosis of hyperchlorhydria and cholecystitis was accepted but in view of his very long history of icterus, with the finding of marked microcytosis of the red cells, chronic hereditary hemolytic jaundice was thought probable.

Case 8.—In 1930 some blood films were sent to us for study by Dr. J. P. Jensen and Dr. R. L. Hamilton, of Sonora, California, from a woman patient of theirs aged 60. The chief complaints for several years past had been dyspnea, dizziness and weakness. The family history contained nothing unusual. The past history was one of long-continued sallowness, inter-

rupted at intervals by definite jaundice. Physical examination was negative except for pronounced pallor and slight icterus. The spleen was not palpably enlarged. Vaginal and rectal examinations were negative. The blood showed 44 per cent hemoglobin, 3,830,000 red cells and 9200 white cells. The most striking feature in the blood films was the measurement of the erythrocytes, which gave an average diameter of 6.6 microns. In view of the long history and recurrent jaundice, with anemia and marked microcytosis, it seemed probable that the condition was one of chronic hereditary hemolytic jaundice. But the patient could not be traced subsequently in order to carry out more complete examinations of the blood.

Summary. In one family 3 cases of chronic hereditary hemolytic jaundice are presented, with notes on 5 other isolated cases with whom contact has been made and the disease has been discussed in the light of reports in the literature.

The importance of the small size of the erythrocytes and their lessened resistance to hypotonic salt solution has been stressed.

REFERENCES.

1. Minkowski, O.: Verhandl. d. Kongr. f. inn. Med., Wiesbaden, 1900, **18**, 316.
2. Hayem, G.: Presse méd., 1898, **6**, 121.
3. Chauffard, A., and Fissinger, C.: Semaine méd., 1907, **27**, 551. Chauffard, A.: Ibid., 1908, **28**, 49. Chauffard, A., and Troisier, J.: Ibid., 1909, **29**, 95.
4. Widal, F.: Semaine méd., 1907, **27**, 586. Widal, F., Abrami, P., and Brule, M.: Presse méd., 1907, **15**, 641; Arch. d. mal. d. coeur, d. vaisseaux et d. sang, 1908, **16**, 193; Cong. Français d. Lyon, Deuxième Session, 1911, Rapports, **12**, 232.
5. Tileston, W., and Griffin, W. A.: Am. J. Med. Sci., 1910, **139**, 847.
6. Meulengracht, E.: Der chronische hereditäre hämolytische Ikterus, Leipzig, 1922 (Verlag von Dr. Werner Klinkhardt).
7. Gänsslen, M.: Deutsch. Arch. f. klin. Med., 1922, **140**, 210; 1925, **146**, 1; Klin. Wchnschr., 1927, **6**, 929.
8. Pemberton, J. deJ.: Ann. Surg., 1931, **94**, 755.
9. McCarty, W. C.: Proc. Staff Meetings, The Mayo Clinic, 1932, **7**, 187.
10. Sjövall, E., and Ivarsson, G.: Finska Läkare-Sällskapets Handlingar, 1929, **71**, 886 (quoted by Beckman and Jäderholm, *q. v.*).
11. Guizetti, P.: Beitr. z. path. Anat. u. z. allg. Path., 1912, **52**, 15.
12. Sisto, P. R.: La clin. med. italiana, 1914, No. 7; Ref. Fol. Hematol. Zentralorgan, 1916, **17**, 156.
13. Friedman, L. J.: Am. J. Roentgenol., 1928, **20**, 440.
14. Wade, R. B., and Steigrad, J.: Med. J. Australia, 1928, **2**, 530.
15. Neuburger, J.: Deutsch. med. Wchnschr., 1931, **57**, 969.
16. Escudero, P., and Varela, M. E.: Rev. Méd. Latino-Amer., 1929, **14**, 1011.
17. Eppinger, H.: Klin. Wchnschr., 1930, **9**, 10.
18. Seelig, S., and Jaffe, K.: Ibid., 1930, **9**, 840.
19. Gänsslen, M.: Ibid., 1930, **9**, 1308.
20. Sear, H. R.: Med. J. Australia, 1928, **2**, 531.
21. Gänsslen, M.: Deutsch. Arch. f. klin. Med., 1922, **140**, 210.
22. Krumbhaar, E. B.: J. Lab. and Clin. Med., 1922, **8**, 11.
23. Baty, J. M.: Am. J. Med. Sci., 1930, **179**, 546.
24. Reynolds, G. P.: Ibid., p. 549.
25. Gänsslen, M.: Loc cit.; Deutsch. Arch. f. klin. Med., 1925, **146**, 1.
26. Haden, R. L.: J. Lab. and Clin. Med., 1931, **16**, 976.
27. Pijper, A.: Lancet, 1924, **2**, 367.
28. Eve, F. C.: Brit. Med. J., 1928, **1**, 941.
29. Cheney, G.: Calif. and West. Med., 1931, **34**, 40.
30. Pijper, A.: J. Path. and Bact., 1931, **34**, 771.
31. Parker, F. P., Lewis, G. T., and McGree, J. L.: J. Lab. and Clin. Med., 1929, **14**, 663.
32. Price-Jones, C.: Brit. Med. J., 1910, **2**, 1418.
33. Von Boros, J.: Wien. Arch. f. inn. Med., 1928, **12**, 243.

34. Wyckoff, H. A.: Unpublished work, Stanford Clinical Laboratory.
35. Haden, R. L.: Arch. Int. Med., 1932, **49**, 1032.
36. Jörgensen, S., and Warburg, E. J.: Acta med. Scandin., 1927, **66**, 109.
37. Cheney, G.: The Morphology of the Erythrocytes in Cirrhosis and Other Diseases of the Liver, Calif. and West. Med., 1933, **39**, 2.
38. Baty, J. M., Blackfan, K. D., and Diamond, L. K.: Am. J. Dis. Child., 1932, **43**, 667.
39. Vaquez, H., and Giroux, R.: Bull. et mém. Soc. méd. d. hôp. de Paris, 1907, **24**, 1184; Semaine méd., 1907, **27**, 551.
40. Micheli, F.: Wien. klin. Wchnschr., 1911, **24**, 1269.
41. Beckman, T. M., and Jäderholm, K. B.: Acta chirurg. Scandin., 1931–1932, **69**, 353.
42. Herfarth, H.: Ergebn. d. Chirurg. u. Ortopaedie, 1926, **19**, 285.
43. Hellström, N.: Quoted by Beckman and Jäderholm (ref. 40).
44. Krumbhaar, E. B.: Physiol. Rev., 1926, **6**, 160.
45. Jedlicka, V., and Varadi, S.: Ztschr. f. klin. Med., 1931, **118**, 286.
46. Ordway, T., and Gorham, L. W.: Oxford Monographs on Diagnosis and Treatment, 1930, **9**, 164—Diseases of the Blood.

THE INTER-RELATION OF CUTLER, LINZENMEIER AND WESTERGREN SEDIMENTATION TESTS.

By Esther M. Greisheimer, M.D. Ph.D.,
ASSOCIATE PROFESSOR OF PHYSIOLOGY,

Alan E. Treloar, PhD.,
ASSISTANT PROFESSOR OF BIOMETRY,

AND

Mary Ryan,
MEDICAL TECHNICIAN, UNIVERSITY OF MINNESOTA, MINNEAPOLIS, MINN.

(From the Department of Physiology and Biometric Laboratory, Department of Botany, University of Minnesota, Minneapolis, Minn.)

Introduction. The possibilities of the blood sedimentation test in diagnosing pathologic conditions and physiologic changes in the human system have led us for several years to conduct investigations of certain phases of this measure. Attention has been drawn elsewhere[1] to the several modifications of technique in vogue at the present time for measuring this phenomenon. Undoubtedly many who have wished to compare results arising from any one method with those accruing from the use of a different technique have shared our experience and found it difficult to do so. It seemed advantageous, therefore, to analyze the relationship between the results of various methods as applied to the same patients in an attempt to provide suitable tables for translating the measure obtained by any one method into comparable measures that might be expected to arise through employing the alternative sedimentation procedures.

Of the many techniques of making the sedimentation test, the Cutler,[2] the Linzenmeier[3] and the Westergren[4] methods appear to

have the greatest number of followers. This paper will be limited to a comparison of the results of these techniques.

The short stout tube (11.2 mm. internal diameter) used in the Cutler method requires 0.5 cc. of 3 per cent sodium citrate and 4.5 cc. of blood. The Linzenmeier method, using a short narrow tube (5 mm. internal diameter), requires 0.2 cc. of 5 per cent sodium citrate and 0.8 cc. of blood. The liquid columns as formed in these two types of tube are of the order of 55 mm. and 44 mm. respectively. The Westergren method calls for a long narrow pipette, into which is drawn to a height of 200 mm. a mixture of 0.25 cc. of 3.7 per cent sodium citrate to every 1 cc. of blood. Thus the three methods differ widely in diameter and length of the fluid column, and in concentration of the anticoagulant. Also the Linzenmeier method calls for measurement of the time required for a sedimentation of 18 mm., while the Cutler and Westergren techniques employ as indices the length of clear plasma at the end of 1 hour of sedimentation. While these differences appear to be simple, considered individually, they provide collectively a complex that is difficult of resolution in terms of differences in the indices.

Experimental Data. The present study is confined to a group of 99 men and 102 women. The subjects, who were chosen without respect to age or health, were University students and ambulatory patients attending the Outpatient Department of the University Hospital. The sedimentation of each sample of blood was studied simultaneously by the original Cutler (5 cc.), the Linzenmeier and the Westergren methods.

In order to insure thorough mixing of the heterogeneous system before commencement of the analysis, it was necessary that the blood for the Westergren test be kept in storage tubes of wider diameter than the pipette until all of the samples for the day had been drawn. At that time the Westergren pipettes were filled from the gently shaken tubes and placed in the racks, the Cutler and Linzenmeier tubes inverted twice, and the tests begun. While it is recognized that possibly it would have been desirable to start the test for each subject as soon as the blood was drawn, such a procedure was not feasible with the assistance available. Hence storage of the blood aliquots in the anticoagulant solution for periods of time up to 1 hour was involved before the sedimentation rate was subjected to measurement. However, our past experience would indicate that the influence of this delay is very small and undoubtedly negligible for the present purposes. Readings were taken at the following intervals of time: 30 minutes, 1, 2 and 6 hours, with a final reading varying between 16 and 18 hours after commencement of the tests. In addition, the time required to reach the 18-mm. mark in the Linzenmeier tubes was determined. If more than 2 hours was required for the latter, the time was calculated by interpolation between the 2-hour reading and a subsequent one.

Due allowance in interpretation must be made for certain cases of an "abnormal" character which may be anticipated to be present in this group. In such individuals the sedimentation proceeds with such rapidity that a pronounced retardation in rate of fall is realized within 1 hour due to "packing" of the erythrocytes at the bottom of the small tubes. Because a sedimentation of 18 mm. or more in 1 hour by the Linzenmeier technique is usually taken to designate a subject of "abnormal" condition, those cases showing a sedimentation index of 18 mm. or over by the Linzenmeier method, or its equivalent by the Cutler and Westergren techniques, have been designated as "abnormal" and removed from the series for the univariate studies. The "normal" subjects of the group, so selected, comprise 86 women and 93 men.

The term "sedimentation index" will be applied herein to the length of clear plasma above the erythrocyte column at the end of 1 hour, regardless of the method. "Sedimentation time" will be applied to the measure of time taken to reach the 18-mm. mark as is designated for the Linzenmeier technique.

Results. 1. *The Univariate Distributions for Sedimentation Index.* As statistics characterizing distribution of the blood sedimentation for the subjects considered, the means and standard deviations may be employed as measures of type and dispersal respectively. These statistics, together with the proportionate fall in 1 hour, are given in Table 1 for the "normal" subjects. From the columns of means it would appear that the average indices arising from the three methods are reasonably concordant, especially when the differences in tube dimension and concentration of anticoagulant are taken into consideration.

TABLE 1.—STATISTICS FOR SEDIMENTATION INDEX (IN MM.) BY THE CUTLER (*C*), LINZENMEIER (*L*) AND WESTERGREN (*W*) METHODS ("NORMAL" SUBJECTS ONLY).

Group.	Mean.			St. deviation.			Index 16-hr. reading		
	L	*C*	*W*	*L*	*C*	*W*	*L*	*C*	*W*
93 men . . .	5.65	6.05	6.75	3.51	4.74	6.28	0.27	0.32	0.13
86 women . . .	10.10	11.03	13.94	3.32	4.05	6.98	0.43	0.49	0.19

A study of the magnitudes of the differences between the means within the sexes, considered in relation to their probable errors, is summarized in Table 2. The comparisons show that the observed differences are undoubtedly significant for the women and probably so for the men. The signs of these differences suggest that the Linzenmeier technique gives, on the average, indices of a lower magnitude than those by the other two methods, the Westergren method yielding indices of the highest average value.

TABLE 2.—COMPARISON OF MEAN SEDIMENTATION INDICES BY THE THREE METHODS.

Group.	C—L		W—L		W—C	
	Mean diff.	P*	Mean diff.	P*	Mean diff.	P*
93 men	+0.41±0.12	0.027	+1.11±0.23	0.001	+0.70±0.17	0.005
86 women	+0.93±0.13	$<10^{-5}$	+3.84±0.31	$<10^{-8}$	+2.91±0.26	$<10^{-8}$

* Probability that the difference is due to chance.

From the ratio of the 1-hour reading to the final reading made (16 to 18 hours), it appears that the blood sediments *relatively* faster in the first hour by the Cutler method than by the Linzenmeier method, and is much slower in the long, narrow Westergren pipette.

The slower sedimentation rate for men than for women has been demonstrated previously for normal adult individuals[5, 6] and for tuberculous patients.[7] The same characteristic is clearly shown for the present series of subjects, the mean indices for the men being but one-half (approximately) of those for the women.

In variability of results, the data show for both sexes a much greater dispersal of indices for the Westergren technique, the Linzenmeier indices being somewhat less variable than those arising from the use of the Cutler method. We reserve for another time the consideration of the relative merits of the methods on the basis of the dispersal of results that they yield.

2. *The Bivariate Distributions and Their Regressions.* No matter in what terms or on what scale the results of tests by two methods are expressed, the degree of relative concordance of the results of the two methods of measurement may be expressed in terms of the correlation between the results. Such measures of association may frequently be employed as direct stepping stones to the formation of the prediction or "regression" equations which give the most likely value that may be expected from the use of one of those methods when the value given by the other method is known. However, if the true regression be neither rectilinear nor parabolic, the method of fitting the regression rarely springs from the use of the usual measures of correlation. Customarily such a regression is empirically selected, so far as type is concerned, by the statistician according to his own judgment, and fitting is proceeded with by the methods of "moments," "least squares," etc., or perhaps by "trial and error."

The experimental data being discussed herein were accumulated primarily to throw light on the relationship between results accruing from the use of different methods of measuring sedimentation in human blood. Since we are concerned with the absolute relationship given by the regression equations rather than with the correlational

measures of concordance, we will pass directly to a discussion of the regressions encountered.

Three general types of regression appear to characterize the relationship between the three methods of measuring sedimentation. The Linzenmeier and Cutler indices appear to be essentially linear functions of each other. Each of these methods has a curvilinear relationship of its indices to those of the Westergren method, the regression being more like a saturation curve than any other form familiar to biologists. The relation of the Linzenmeier time meas-

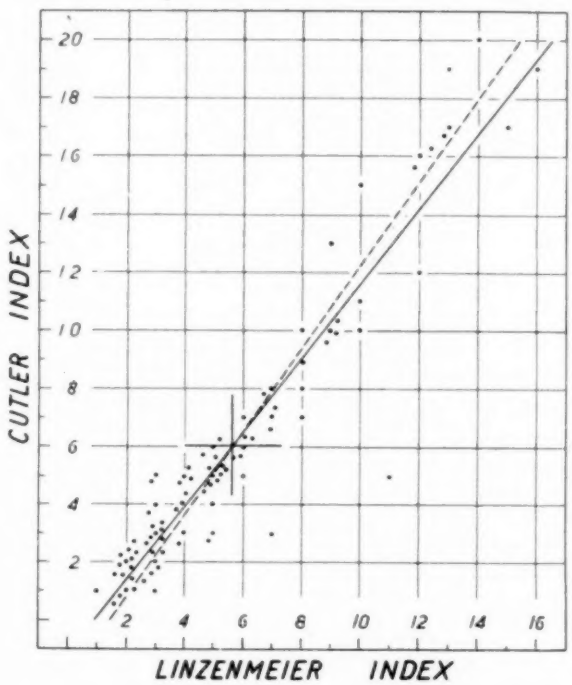


FIG. 1.—Scatter diagram for the interrelation of Cutler and Linzenmeier indices for 93 "normal" men. The full and broken lines respectively trace the loci of the equations for predicting the Linzenmeier index from the Cutler index, and *vice versa*.

ures to the indices by each method is in all cases given satisfactorily by sections of hyperbolæ. The three types are illustrated in Figs. 1 to 3 inclusive.

That straight line prediction should be adequate for practical purposes when applied to the Cutler-Linzenmeier index surfaces is clear from inspection of the typical scatter diagram given in Fig. 1. However, this particular regression is of academic rather than clinical interest because sedimentation by the Linzenmeier method is customarily measured in terms of time and not as an index as defined

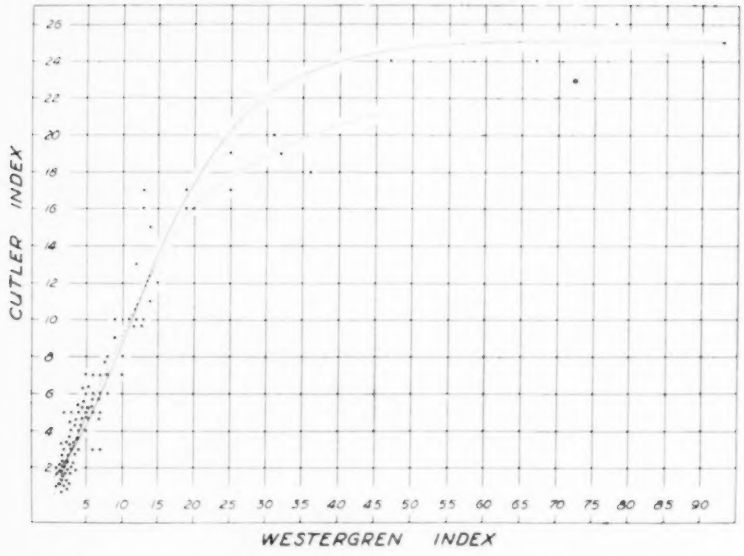


FIG. 2.—Scatter diagram for the interrelation of Cutler and Westergren indices for 99 men. The full line is the best of numerous mathematic functions fitted to the regression of Cutler on Westergren. It is given by the equation: $\log C = 1.4 - 1.3\ (0.9)^{W}$. The broken line is the free-hand graduation employed herein for predicting C from W (see text).

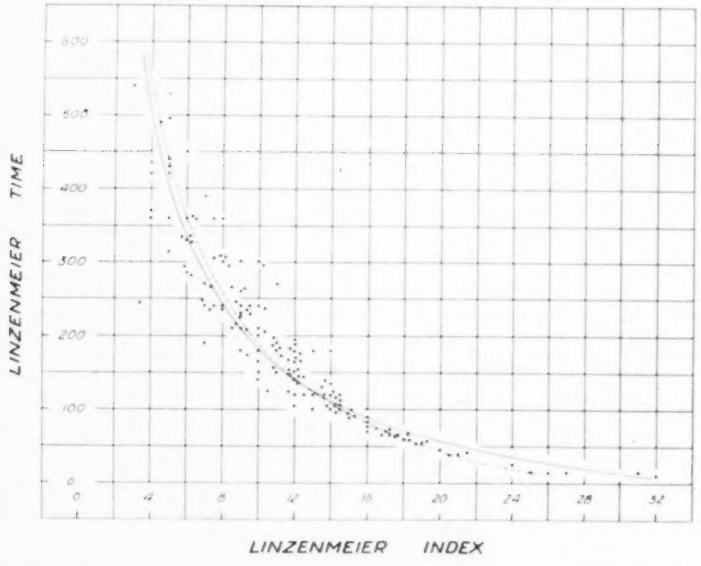


FIG. 3.—Scatter diagram illustrating the hyperbolic regression for the interrelation of the time and index readings for blood sedimentation. The data are for the application of the Linzenmeier technique to 150 women. The full and broken lines are respectively for the prediction of time from index and *vice versa*.

herein (mm. fall in 1 hour). This surface will not be discussed here beyond noting the point that the regressions are not the same, within errors of sampling, for the two sexes. We feel that it is inadvisable, therefore, to consider the two sexes collectively in arriving at the regression lines for the other surfaces, where tests for the significance of differences in the constants are not available, and we report the prediction values in the following tables separately on that account.

The relationship of Cutler to Westergren indices has presented a problem of considerable complexity. The best of numerous mathematical functions experimented with is given by the continuous curve in Fig. 2. It does not provide a satisfactory graduation, and we have been forced to depend on fitting free-hand a line that appeared to agree well with a general scheme of such lines drawn for the ½-hour, 1-hour, 2-hour and 6-hour readings. This line is given by the broken curve in Fig. 2.

The relationships between Linzenmeier time readings and the three indices are satisfactorily given by sections of hyperbolae. These were fitted by the method of "moments," employing the following type of equation:

$$y = \frac{a + bx}{c + x}$$

where a, b and c are constants determined from the data.

Tables 3, 4 and 5 summarize the regression values for each type of measure taken as independent variable and given as the column on the left. The prediction value is given to the nearest whole number only, because we feel that in some cases the results have questionable dependability beyond that figure.

TABLE 3.—FOR THE PREDICTION OF SEDIMENTATION MEASURES FROM THE CUTLER INDEX.

Cutler index.	Westergren index.		Linzenmeier time.	
	M	*F*	*M*	*F*
3	3	3	669	469
4	4	4	581	412
5	5	5	509	365
6	6	6	449	326
7	7	7	399	292
8	9	9	355	263
9	10	10	318	237
10	11	12	285	215
11	12	13	256	195
12	13	15	230	177
13	15	16	207	161
14	16	18	187	147
15	17	20	168	134
16	19	22	151	122
17	21	24	135	111
18	23	27	121	101
19	..	29	108	92
20	..	32	96	83

TABLE 4.—FOR THE PREDICTION OF SEDIMENTATION MEASURES FROM THE WESTERGREN INDEX.

Westergren index.	Cutler index.		Linzenmeier time.	
	M	*F*	*M*	*F*
2	2	2	910	552
4	4	4	548	421
6	6	6	389	339
8	7	8	265	282
10	9	9	244	241
12	10	11	204	209
14	11	12	175	184
16	12	13	153	164
18	13	14	135	136
20	14	15	121	133
22	15	16	109	122
24	16	17	99	111
26	17	18	91	103
28	18	18	84	95
30	18	19	77	88
32	19	20	72	82
34	20	21	67	76
36	20	21	62	71

TABLE 5.—FOR THE PREDICTION OF SEDIMENTATION INDICES FROM THE LINZENMEIER TIME READING.

Linzenmeier time.	Cutler index.		Westergren index.	
	M	*F*	*M*	*F*
700	3	2	3	3
600	4	3	4	3
500	5	4	5	4
400	6	6	6	6
350	7	6	7	7
300	8	8	8	8
260	9	9	10	10
230	10	10	11	11
200	12	11	13	13
180	13	12	15	15
160	14	13	17	16
140	15	14	19	18
120	17	15	23	21
100	19	17	29	25
90	20	18	33	27
80	21	19	38	29
70	23	20	45	32
60	25	21	55	36

We wish also to draw attention in general terms to an important feature of the surfaces which is rather too technical to discuss in detail here. The variability of the individual measures about the lines of average relationship is such as to leave no doubt whatever about the deduction that sedimentation measures for human blood are in part specific for the technique employed. That is, the discrepancy between what happens in individual cases and what is reported here as a general average for the type of patients considered, is not entirely due to errors of measurement.[8] There is considerable need for a careful study of the effects of kind and concentration of the

same anticoagulant in the various diameters of tube and for varying lengths of column of fluid in order that the sedimentation technique may reach its full utility. Standardization of a single method for general use would appear to be most highly advantageous, and we propose to devote attention to this problem in the immediate future.

Summary and Conclusions. Blood sedimentation in 99 men and 102 women, selected without regard to age or health from University students and ambulatory patients, has been studied to establish the inter-relationships between the Linzenmeier, Cutler and Westergren methods. The average sedimentation in 1 hour for "normal" subjects appears to be reasonably concordant for the 3 methods despite the wide differences in tube width, anticoagulant concentration and length of fluid column, although the differences between the means for the 3 methods are significant statistically. The average sedimentation at 1 hour for the women is approximately double that for the men.

The concordance between the results by each pair of methods for the individual patients has been subjected to analysis by preparing the correlation tables. The regression lines, for predicting the most likely value to be expected by any one test when that by another is known, proved to be of three distinct types. There is a rectilinear relationship between the Cutler index and the Linzenmeier index. The regressions between Westergren index and Cutler or Linzenmeier index appear to be somewhat like saturation curves. However, they had to be fitted by a systematic scheme of free-hand graduations for lack of a suitable type of mathematical equation. The relationships between the various indices and Linzenmeier time values may be suitably portrayed by section of hyperbolæ. Tables are provided for these average predictions for each independent variable of clinical interest.

The dispersals of individual cases about the lines of average relationship, although not studied in detail, are clearly greater than those ascribable to errors inherent in the techniques. The conclusion is clear that sedimentation measures for human blood are, in part, specific for the technique employed.

Standardization of a generally acceptable method for blood sedimentation would prove most advantageous for clinical work.

REFERENCES.

1. Cutler, J.: Am. Rev. Tuberc., 1929, **19**, 544.
2. Cutler, J.: Am. J. Med. Sci., 1926, **171**, 882.
3. Linzenmeier, G.: München. med. Wchnschr., 1923, **70**, 1243.
4. Westergren, A.: Am. Rev. Tuberc., 1926, **14**, 94.
5. Greisheimer, E. M.: Am. J. Med. Sci., 1927, **174**, 338.
6. Greisheimer, E. M., Johnson, O. H., and Ryan, M.: Am. J. Med. Sci., 1929, **177**, 816.
7. Greisheimer, E. M., Van Winkle, C. C., and Johnson, O. H.: Am. Rev. Tuberc., 1929, **19**, 559.
8. Treloar, A. E., and Greisheimer, E. M.: Proc. Soc. Exp. Biol. and Med., 1933, **30**, 962.

A STUDY OF STEATORRHEA.

With Special Reference to Its Occurrence in Pancreatic Disease and Sprue.

By Joseph H. Pratt, M.D.,
Professor of Clinical Medicine, Tufts College Medical School; Physician in Chief, Boston Dispensary, Boston, Mass.

(From the Laboratories of Medicine of Harvard Medical School and Tufts College Medical School.)

My interest in disease of the pancreas was aroused thirty years ago by the late Prof. Reginald Fitz while I was assisting him in the study of the literature made in preparation of the notable paper he read at the Congress of Physicians and Surgeons in 1903. Dr. Fitz was one of the first to realize that chemical studies of the feces were necessary in order to get more thorough knowledge of disturbances in pancreatic function. He pointed out that the recognition of steatorrhea "in doubtful cases requires the skill and facilities of the chemist trained in physiologic methods." At that time he was able to find only 8 reported cases of pancreatic disease in which the percentage of fat in the stools had been determined. It ranged from 29 to 46.8 per cent. He listed also 3 cases of catarrhal jaundice with fat in the stools from 9.6 to 44 per cent, and 1 analysis on feces from a healthy subject on a milk diet which showed 21 per cent of the dried weight of the stools to be made up of fat.

Fat, when present in large amounts in the stools, often appears as oil or as masses resembling butter, lard or tallow. It may, on the other hand, be intimately mixed with other fecal material and give to a solid stool a silvery gray appearance like that of aluminum paint. When the surface is compressed or scraped by means of a spatula or knife blade the greasy character of a fatty stool is often made evident. Microscopically, fat occurs in the feces as oil drops, flakes or as acicular crystals. When a bit of fecal material is mixed with a few drops of 30 per cent acetic acid on a glass slide and heated to boiling the flakes and crystals are converted into fat droplets. If much fat is present the preparation seems then to be almost entirely converted into droplets of various size. Fat may be present in the stool in large amounts and yet not be recognized on microscopic examination. The dried feces of a healthy person on a mixed diet contains 25 to 30 per cent of fat and yet little or no fat is demonstrable with the microscope. Sometimes serious errors are made in attempting to determine the amount of fat by gross and microscopic examination. In a case of cancer of the pancreas I once reported that a stool was not fatty and yet analysis showed that 56 per cent of the dry weight was fat. Another stool

from the same patient which seemed on microscopic study to be largely composed of fat was found to contain but 64 per cent of fat. While this was an exceptional case—as usually the results of a careful naked eye and microscopic examination correspond fairly well with the chemical analysis—it is true, as Dr. Fitz pointed out many years ago, that the recognition of some cases of steatorrhea require the careful and time consuming quantitative methods of the chemist.

The results obtained by my associates and myself in the analysis of the feces in 33 cases have been collected. These include all those with fatty stools that we have been able to study and for comparison a few other conditions in which the stools were not fatty, namely, nervous diarrhea and ulcerative colitis.

Fat Content of the Feces. In the series collected by Fitz, the smallest percentage of fat found in the feces was 9.6 per cent—a lower fat content than ever found in health. This was in a case of catarrhal jaundice reported by Katz;[1] but his method—simple extraction of dried feces with ether in a reflux condenser—failed to remove all the fat. The lowest recorded by Schmidt[2]—in a case of so-called gastrogenous diarrhea—was 12.6 per cent. In health on Schmidt's same standard diet the average percentage in the 3 persons he studied was 23.2 per cent, the maximum being 26.6 per cent. In long continued fasting as much as 35.5 per cent of the dried stool has been found to be composed of fat.[3] This fat, as Hill and Bloor[4] have shown, comes from the intestinal secretions.

In only 4 of our 33 cases was there less than 20 per cent of fat in the dried feces. The lowest percentage was 17.4 in a case of acute pancreatic necrosis. No record is available regarding the diet of this patient, but as he was recovering from a laparotomy it was probably restricted and low in fat. The next lowest, 18.4 per cent, was found in 1 case of nervous diarrhea and in the stools of 1 patient after recovery from mild nervous diarrhea. There were 4 of our series with a fat content of the dried feces at the normal level, that is, between 20 and 30 per cent. In this group was a case of nervous diarrhea and 1 of ulcerative colitis. Our lowest percentage of fat with the patient on the Schmidt diet was 18.4 per cent.

There were 9 cases with a fat content between 30 and 40 per cent. Only 1 of our 7 cases of cancer of the pancreas had less than 40 per cent of fat in the stools (36.3 per cent). The diagnosis was verified by autopsy, but the pancreatic ducts were not obstructed. In 3 of our 6 cases of obstructive jaundice it ranged from 30 to 36.8 per cent. In a case of typhoid fever in which the stools looked fatty, 33.5 per cent was found; in a patient with "nervous diarrhea," on the Schmidt diet, there was 34.1 per cent. It is necessary to examine more cases of undoubted nervous diarrhea before the significance, if any, of this rather high percentage of fat is clear, but in the light of our experience it is suggestive either of a chronic enteritis or a

rapid passage of food through the small intestine. One of our 4 cases of sprue had 38.8 per cent of fat in the dried stools, the others more; a second case had 44.1 per cent. This patient was recovering from the disease which had developed a number of years previously in China.

TABLE 1.—ALL CASES ANALYZED IN THE PRESENT SERIES WHICH INCLUDE NERVOUS DYSPEPSIA, JAUNDICE, SPRUE AND PANCREATIC DISEASES.

Per cent of fat in dried feces.	Number of cases.
10 to 20	4
20 to 30	4
30 to 40	9
40 to 50	1
50 to 60	4
60 to 70	6
70 to 80	4
80 to 90	1
Total	33

As had been stated, the highest percentage of fat in dried stools in Fitz's series was 46.8 per cent. This was in a case of cancer of the pancreas with jaundice studied by Northrup and Herter.[5] In our experience, 15 of the 22 cases with grossly recognizable fatty stools contained over 50 per cent of fat. There were 4 cases with between 50 and 60 per cent. Of the 2 with cancer of the pancreas, 1 with obstructive jaundice, while on the Schmidt diet, had 52 per cent of fat in the dried feces; the other without jaundice had 57.9 per cent. In the other 2 in this group with a fat content of the dried stools of 53 and 59.5 per cent respectively, the diagnosis was probably atypical sprue. Of 6 cases with a fat content between 60 and 70 per cent, 3 were cancer of the pancreas, and 2 were cases of steatorrhea undiagnosed. In these 2 there was no evidence of obstruction or of sprue. One patient with proved cholelithiasis, but without jaundice, passed a single fatty stool which on analysis was found to contain 67.5 per cent of fat—probably due to transitory occlusion of the common bile duct.

Of the 4 cases with over 70 per cent fat in the dried feces, 1 was sprue (on the Schmidt diet, 78.4 per cent), 2 were obstructive jaundice (73.3 and 78.2 per cent, respectively), and the 4th was cancer of the pancreas (72.8 per cent).

The single case with more than 80 per cent fat was one of sprue (on the Schmidt diet, 86.2 per cent fat).

The highest percentage of fat in the feces observed by Schmidt on his diet was in a case of obstructive jaundice in which the feces contained 53.6 per cent. In 2 other cases of this disease he found 43.9 and 48.5 per cent. Thus he had only 1 case with more than 50 per cent of fat as compared to 15 (6 of cancer of the pancreas, 3 of sprue, 3 of obstructive jaundice and 3 of steatorrhea of unknown etiology).

Fat Splitting and Soap Formation. Fat occurs in the feces in the form of neutral fat, fatty acids and soaps. As the fat is held to be split chiefly by the steapsin of the pancreatic juice into fatty acids and glycerin, it would seem probable that when no pancreatic juice enters the duodenum there would be an increased percentage of unsplit fat found in the feces. The early observations of Müller[6] on 3 cases supported this view; it is probable, in the light of later investigations, that in his cases the pancreatic juice was not absent or even deficient. Since then in undoubted instances of complete absence of pancreatic juice, with few exceptions, the fat in the feces has been found well split. In depancreatized dogs Abelmann[7] found no excess of neutral fat in the stools, nor did Pratt, Lamson and Marks[8] in dogs in which all pancreatic juice was excluded from the intestine by separating the pancreas from the duodenum. In one of their experiments there was only 18.4 per cent of neutral fat, although there was no pancreatic secretion entering the intestine, while in a dog in which the operation had failed, the neutral fat made up 59.4 per cent of the total fat in the stools.

In our study of 6 cases of chronic pancreatic disease, all probably cancer of the pancreas, the average percentage of neutral fat in the fecal fat was only 35. This was less than Schmidt found in his 3 normal subjects, as his average was 40 per cent. The largest percentage of neutral fat found by us in pancreatic disease was 56.8—in a patient on the Schmidt diet with complete obstruction of the pancreatic ducts without icterus. No especial significance can be attached to this finding, as Tileston, in a further study of the same patient on a mixed diet, found only 35.8 per cent neutral fat, and on a fat-restricted diet, just a month after ours, only 14.1.

The largest percentage of neutral fat I have found was in a patient (Schmidt diet) with nervous dyspepsia (71.1 per cent). The smallest percentage of neutral fat among all our cases was 14—singularly enough this was in a fatty stool passed by a patient who had a cancer of the pancreas.

It is evident from these figures that the percentage of neutral fat in the stools is of no aid in the diagnosis of pancreatic or other diseases.

Zoja[9] looked upon a low percentage of *soaps* in the feces as an important indication of deficient pancreatic secretion. Tileston[10] placed the normal percentage at 40. Deucher,[11] in a case of obstruction of the pancreatic ducts, found only 7 per cent of the fecal fat in the form of soaps, Ehrman[12] 15, Brugsch[13] 8, and Tileston, in 1 case, 5 per cent. When Tileston gave calcium carbonate, 0.6 gm. daily, the percentage of soaps rose to 49. My lowest percentage was 4—in the case of obstruction of both pancreatic and common bile ducts. When in a second test pancreatic ferment without alkalies was given, the percentage of soaps rose to 30. In the same patient which Tileston studied, Morrison and I had previously

found 6 per cent of the fecal fat in the form of soaps with the patient on the Schmidt diet. In another case of cancer of the pancreas there was only 9.8 per cent of soaps. In non-pancreatic diseases I have never seen such low percentages. The soaps, however, in patients with normal pancreatic digestion may be much less than the fatty acids. In a case of sprue there was 26 per cent of fatty acids and only 19 per cent of soaps. A high percentage of soaps does not rule out pancreatic disease as a cause of steatorrhea, as in 1 case of cancer of the pancreas (confirmed at autopsy) the soaps made up 55 per cent of the fecal fats.

A knowledge of the percentage and amount of fat absorbed from the food is of far greater value in diagnosis than a determination alone of the percentage of the fat in feces. Knowing the latter without the former is much like attempting to estimate the value of a fraction from the numerator alone. For example, Mrs. M., a patient with a diarrhea resembling sprue, during a 3-day period on a milk diet passed stools which, when dried, were found to be 59.5 per cent fat. This fat content is very high, but as the dried weight of the feces was only 107 gm., the fat excreted was only 63.7 gm. As the milk diet contained 190 gm. of fat the fat loss was 33.5 per cent of the fat consumed. Prof. G., a patient with obstruction of the pancreatic ducts and icterus, during a test period had stools containing 52 per cent fat. Although the feces thus contained 7.5 per cent less fat than those of Mrs. M., the amount of the dried feces was so great (419 gm.) that the amount of fat lost to the body was nearly $3\frac{1}{2}$ times that in the other case, or 65.5 per cent of the fat in the diet.

Method. For our study we have employed the test diet recommended by Schmidt, except in cases of sprue. Here we preferred a strict milk diet, as better borne by the patients. This standard test diet has enabled us to compare our results with those obtained by Schmidt and other workers in this field. As it appears in different works variously modified, yet bearing the name of the Schmidt diet, it is important to state that the diet we used conformed exactly to instructions given by Schmidt, as follows: Mornings: 0.5 liter of milk, with 50 gm. zwieback. Forenoons: oatmeal gruel (40 gm. rolled oats, 10 gm. butter, 200 gm. milk, 300 gm. water and 1 egg, and salted to taste—strain). Noon: 125 gm. finely chopped roast beef (raw weight) lightly broiled, *so that the interior remains uncooked.* In addition, 250 gm. potato purée (made of 190 gm. potato, 100 gm. milk and 10 gm. butter, salted to taste). Afternoons: as mornings. Evenings: as forenoon.

This daily diet contains, according to Schmidt, 102 gm. protein, 111 gm. fat and 191 gm. carbohydrates. This yields 2234 calories (computed from Koenig's tables). Analysis of this diet made by Harley and Goodbody[14] gave slightly different results: 118 gm. protein, 105 gm. fat, 204 gm. carbohydrates; together, 2297 calories. The average of 5 analyses made in our laboratory gave protein, 102 gm.; fat, 132 gm., and carbohydrates, 180 gm., with a caloric value of 2324.

This diet is given for 3 days. To mark off the stools 0.3 gm. of carmine is taken with the first meal. The feeding period ended, we give on the following morning charcoal with a breakfast consisting wholly of milk.

The charcoal is best given in the form of an emulsion (℞—Carbo vegetab., 15 gm.; mucilago gummi arab., 15 gm.; aq. menthae pip., 60 cc.). Of this, 3 teaspoonfuls are taken. After the beginning of the test diet the first stool colored red with carmine is saved, and collections continued until charcoal appears. The first stool colored with charcoal is rejected. The feces of a normal person taking the Schmidt diet has a uniform consistence and a light brown color.

Chemical Methods Used. The feces to which alcohol was added were dried over a water bath to constant weight. Nitrogen was determined by the Kjeldahl method. Fat was extracted by the Soxhlet apparatus or Saxon method. The method of Folin and Wentworth was largely employed. To determine the amount of starch the dried feces were first digested with 2 per cent HCl and then decolorized with Lloyd's reagent. In the filtrate the sugar was determined by Folin's method for blood sugar.

Weight of the Stools in Health and Disease. Observations made by Schmidt on 5 normal persons gave 54.3 gm. as the average weight of the dried stools obtained from his diet during a 3-day period (maximum weight, 62; minimum, 45 gm.). The lowest weights occur in chronic constipation. The average weight in observations made by Lohrisch[15] and Tomaszewski[16] on 6 patients with constipation taking the Schmidt diet was 33.3 gm. The amount of dried feces was quite constant in these cases, ranging from 30 to 37 gm.

In 19 absorption studies for 3-day periods on 17 different patients taking the Schmidt diet, we have found that the weight of the dried feces was greater in the various types of steatorrhea than in other conditions (Table 2).

TABLE 2.—WEIGHTS OF DRIED FECES OF PATIENTS ON SCHMIDT DIET.
(*Three-day Period on the Schmidt Diet.*)

Case.	Name.	Disease.	Weight of dried feces, gm.
1	Mr. Pe.	After recovery from mild nervous diarrhea	45.0
2	Mr. M.	Recovering from jaundice	68.0
3	Mrs. S.	Ulcerative colitis	74.5
4	Mr. Tu.	Nervous diarrhea	77.0
5	Miss C.	Nervous diarrhea	79.5
6	Mr. Co.	Nervous diarrhea	82.2
7	Mr. T.	Nervous diarrhea	83.0
8	Mr. Ba.	Biliary cirrhosis with slight icterus	91.0
9	Mr. B.	Steatorrhea of unknown origin (period with pancreatic ferments added to diet)	124.0
10	Miss M.	Steatorrhea of unknown origin	130.0
11	Mrs. Ma.	Obstructive jaundice	131.0
9	Mr. B.	Steatorrhea of unknown origin (period without pancreatic ferments)	143.0
12	Mr. C.	Sprue	149.0
13	Mrs. P.	Chronic enterocolitis	167.0
14	Mrs. D.	Chronic obstructive jaundice	221.0
15	Mrs. W.	Sprue	269.0
16	Prof. G.	Obstruction of common bile and pancreatic ducts (with pancreatic ferments added to diet)	355.0
16	Prof. G.	Without pancreatic ferments	419.0
17	Mr. Mc.	Obstruction of pancreatic ducts	438.0

From Case 8 onward in this list, all had fatty stools except Case 13, whose feces contained only 19 per cent of fat. In a severe case of enteritis studied by Schmidt, the dried feces weighed 186.5 gm., nearly 20 gm. more than in our Case 13. One of our cases of obstructive jaundice without pancreatic involvement had a little larger amount of dried feces, 221 gm., than Schmidt obtained in any of his 3 cases, which averaged 191.8 gm. The average in our 2 cases was 176 gm. The heaviest weight Schmidt records was 215 gm., in a case in which the bile was completely excluded from the intestine.

It will be noted that 4 of our patients fed the same amount of food as that given by Schmidt passed larger amounts of solid material than any in his series. The figures given in this table substantiate the statement the writer made many years ago that the weight of the dried stools with the patient on the Schmidt diet is of diagnostic importance. A large amount of dried feces in our experience indicates poor absorption of fat or nitrogen, or both.

Two absorption studies were made when the diet consisted only of milk. A patient with sprue, Mrs. H., when given 2200 cc. of milk daily, passed feces during the 3-day period which weighed, when dried, 109 gm. A patient with steatorrhea of unknown origin (Case 10), when given a total of 5600 cc. of milk during the test of 3 days' duration, passed feces weighing 107 gm.

Absorption of Fat in Cases of Steatorrhea. Normally over 94 per cent of the fat in the Schmidt diet is absorbed; the average in 3 cases being 94.5 per cent (Schmidt). In 7 of our cases over 90 per cent of the fat was utilized. In this group there was only 1 of undoubted organic disease of the intestine, the other 6 being chronic diarrheas of nervous origin. The patient that showed the best absorption (97.9 per cent) in our entire series had just recovered from a mild neurogenic diarrhea. In our 2 cases of obstructive jaundice due to gall stones there was 56.2 and 81.2 per cent of fat absorbed. Schmidt's figures of fat absorption in obstructive jaundice are 77.2, 82.3 and 72.8 per cent (average, 74.1). These represented the highest disturbance in fat absorption that came under his observation. He had no cases of sprue or of pancreatic disease with obstruction of the ducts. His personal experience explains his assertion that "the highest fat content of the feces and the greatest percentage of fat loss occurs when bile is excluded from the intestine." The error in this statement is apparent from our finding that 4 of our patients with no obstruction to the flow of bile into the intestine had greater fat losses than he ever observed in obstructive jaundice. These were cases of sprue and obstruction of the pancreatic ducts. In all these, the fat lost in the feces was over 25 per cent. It is quite possible that in our case of obstructive jaundice, in which 81.2 per cent of the fat in the diet was utilized, some bile was passing into the duodenum around the gall stone that was found at operation blocking the common bile duct. The absence of bile in the feces, as

demonstrated by the corrosive sublimate test of Schmidt[17] for bile pigments, is not proof that no bile is entering the intestine. It is necessary for this purpose to demonstrate by duodenal drainage, as Wendt[18] has shown, that the duodenum contains no bile, but this evidence was not obtained in our case just cited nor in those of Schmidt. In our other case of obstructive jaundice without pancreatic disease in which the fat absorption was only 56.2 per cent, bile was absent in the duodenal contents.

The first exact studies of fat absorption in icterus were made by Müller.[6] In complete obstruction of the common bile duct he found that between 55.1 and 78.8 per cent of the fat fed was recovered from the stools. Brugsch[13] found on the average about 45 per cent of the fat fed was unabsorbed in complete jaundice. He held that if fat loss in the stools amounted to 60 per cent or more of the ingested fat, there was probably also involvement of the pancreas present. He later modified this to read that more than 60 per cent of the fat fed might be lost in icterus without pancreatic disease, but only when severe disease of the liver, usually malignant, or of the small intestine coëxisted. It is certainly true that in one disease involving the small intestine, sprue, great losses of fat in the stools regularly occurs. I have never observed steatorrhea in any other disease of the intestine or in any disease of the liver unassociated with biliary disease. It has been shown by Gutzeit and Wendt[19] that a disturbance in the fat absorption can be demonstrated in chronic gastro-enteritis and cirrhosis of the liver by a fat tolerance test consisting of the feeding of very large amounts of fat—that is, 340 to 460 gm. daily. The relation of their studies to the clinical occurrence of steatorrhea is not apparent, owing to the large amount of fat required to demonstrate any disturbance in absorption. My own experience convinces me that if the fat loss in jaundice is above 45 per cent, one should always suspect the simultaneous involvement of the pancreas. In our only case of obstructive jaundice combined with occlusion of the pancreatic ducts, 65.5 per cent of the fat in the Schmidt diet was excreted in the stools. A second period on the same patient showed the largest fat loss I have ever observed—66.2 per cent. Mild hepatitis may certainly produce a disturbance in fat absorption that is transitory. A patient recovering from so-called catarrhal jaundice, in whom the icterus disappeared only a day or two before the Schmidt diet was given, had a fat loss of but 6.1 per cent, although the day before the test was begun the stools contained an excess of fat on microscopic examination.

In our only case of complete obstruction of the pancreatic ducts without icterus the fat loss on the Schmidt diet was 58.9 per cent. The stools were light yellow, soft and fatty and voluminous. Admixed with the feces were large masses of fat looking like butter. The dried feces over the period of 3 days weighed 438 gm.—the

largest amount ever recorded on the Schmidt diet, so far as I can find. V. Noorden,[20] however, states that 1 of his cases of pancreatic disease, the weight of fresh feces was 1500 to 2000 gm. daily.

Steatorrhea is the most characteristic symptom in tropical sprue and one that enables this disease to be easily distinguished from pernicious anemia and pellagra. In 7 cases of sprue, Van der Scheer[22] found that with the patients on a mixed diet the fat content of the dried feces ranged from 29 to 55 per cent. In a fat utilization experiment he found that with the patient taking 60 gm. of fat in the diet, 21.8 per cent was lost in the stools. Schmidt, in a case of sprue, found in the feces 65.2[24] per cent of the fat fed, while normally only 5 to 8 per cent is unabsorbed, in fact less, as some of the fat in the feces as Hill and Bloor[21] have shown is secreted from the intestine. Similar if less marked disturbance in the absorption of the fat in sprue have been obtained by others.[22] In 2 of my patients with sprue that were tested with the Schmidt diet the loss of fat in the stools was 32.9 and 45.1 per cent. In a 3d case on a milk diet the feces contained 18.9 per cent of the fat fed, and in a 4th case of steatorrhea possibly due to sprue the loss of fat was only 11.8 per cent on the Schmidt diet and 33.5 per cent on a milk diet. This case is more properly classed as steatorrhea of unknown origin. After the patient left Boston she developed ascites and subsequently died; no autopsy was obtained.

In 1908 Pratt and Hatch[23] reported a case of what was probably sprue in a paper entitled, "On the Occurrence of Steatorrhea Unassociated with Jaundice or Demonstrable Pancreatic Disease." At the time neither we nor any of the physicians of the hospital were familiar with the symptoms of sprue, and this diagnosis was not suggested by anyone while the patient was under observation. The patient developed a chronic diarrhea in Puerto Rico where he had lived for many years. A year after the onset, when he came to Boston, he was having 1 to 10 stools daily. They were bulky, light yellow, semi-solid and often frothy. The fat content of 1 of the stools was 53 per cent. Unfortunately an absorption study was not made. The patient had a slight anemia; the erythrocytes being 3.5 million per c.mm. and the hemoglobin 80 per cent. There was no complaint of a sore tongue, but inquiry on this point was apparently not made in the past, and the note on the status praesens did not record appearance of the tongue. In view of the frequency of sprue in Puerto Rico and the rarity of fatty diarrhea in other conditions unassociated with icterus, this diagnosis is most likely. The patient reported a month after leaving the hospital that the diarrhea had ceased.

Steatorrhea of Undetermined Origin. We have had 3 cases of fatty diarrhea without icterus in which there was no evidence of pancreatic disease, tuberculosis or sprue. It has been known for many years that in tabes mesenterica the lacteals may be occluded and

steatorrhea result. Schmidt studied 2 cases of tuberculosis of the mesenteric lymph nodes in which the average fat content of the feces was 32 per cent during the test period on his diet and the average fat loss 17 per cent. Müller, in 1 case of amyloidosis of the intestine, obtained 32.9 per cent fat loss and Weintraud, in progressive tuberculosis of the intestine, 30 to 37 per cent. In one of the cases of steatorrhea studied by Morrison and myself tuberculosis of the mesenteric lymph nodes was excluded by an exploratory laparotomy. The pancreas was examined and found to be normal in appearance. The patient died soon after leaving the hospital; autopsy was refused. This patient, in a 5-day period on the Schmidt diet, excreted 24 per cent of the fat contained in the food. In a second period of the same duration 12 pancreon tablets were given daily, but the fat absorption was not increased. Indeed, the fat loss was slightly greater, amounting to 25.7 per cent. The fat content of the feces obtained in the two tests was 56.8 and 66.4 per cent.

Nitrogen Absorption an Aid to Diagnosis in Steatorrhea. The presence of many undigested muscle fibers in the stools is a characteristic feature in pancreatic disease when the ducts are occluded, and is visible evidence that some of the nitrogen of the meat in the diet is undigested and, as a result, is lost to the body. Chemical analyses show that this loss of nitrogen is great in the absence of pancreatic juice from the intestine. After separating the pancreas from the duodenum and thus excluding all pancreatic external secretion, Pratt, Lamson and Marks[8] found that a nitrogen loss in the feces was of constant occurrence and of high degree, amounting to from 38.3 to 77.8 per cent of the nitrogen content of the food. Recent studies in our laboratory show that, while in dogs deprived of pancreatic digestion the fat loss can be largely prevented by changes in the diet, a considerable nitrogen loss persists with all diets.

Our clinical observations show that this faulty absorption of nitrogen is of greater value in the recognition of pancreatic disease than is the faulty absorption of fat. In the other forms of steatorrhea studied, the loss of fat to the body is not associated with so marked a loss of nitrogen. In our 2 cases of obstructive jaundice, 93 and 92 per cent of the nitrogen of the Schmidt diet were utilized. This is within normal limits. Schmidt does not give the nitrogen absorption of healthy subjects placed on his diet and we have made no determinations on normal persons. However, in 1 of our patients who had only a slight tendency to looseness of the bowels, the nitrogen absorbed on the Schmidt diet was 95.8 per cent, and in 3 cases of nervous diarrhea over 92 per cent of the nitrogen of the food was absorbed.

In sprue, as we have shown, the fat loss in the stools may be great, even exceeding that seen in some cases of pancreatic disease

with incomplete obstruction of the ducts. The nitrogen absorption, on the other hand, may be little, if at all, disturbed. In 2 cases of sprue on which we made absorption studies with the patient on the Schmidt diet the utilization of nitrogen was 86.6 and 90.4 per cent. In a third case on a milk diet the nitrogen absorption was 99.1 per cent—the highest we have ever seen. A study of the literature shows that in some cases of sprue a considerable loss of nitrogen in the feces occurs. In a case of Schmidt[24] it amounted to 28.7 per cent, and in one studied by v. Noorden,[25] to 18.2 per cent. In 2 of our cases of steatorrhea of unknown origin the nitrogen absorption was 84 and 88.9 per cent. In the second of these cases on a milk diet, 98.3 per cent of the nitrogen of the milk was absorbed, while the fat absorption was only 66.5 per cent. These findings are very different from those obtained in pancreatic disease and resemble those we found in sprue. The diagnosis of sprue was not justified, however, as the other characteristic features of this disease were lacking.

The percentage of nitrogen in the dried stools has proved of no definite value in diagnosis, as an analysis of the results in 33 cases shows. It has ranged from 1.4 to 8 per cent; in only 7 cases was it 5 per cent or more. The highest nitrogen content, 8 per cent, was, however, in the feces from a case of cancer of the pancreas. The same stool had a fat content of 72.8 per cent. In a patient with complete absence of pancreatic digestion the nitrogen content of the feces with the patient on the Schmidt diet was 5.8 per cent. This has no particular significance, as Rubner[26] found 8.3 per cent of nitrogen in the dried feces of a healthy subject when fed on white bread, 7.9 per cent when given a diet of rice, and 6.9 per cent when the food was macaroni. Table 3 shows that even when the fat content of the stools in cancer of the pancreas is great, the percentage of the nitrogen may be low and that there is no definite relation between the two.

TABLE 3.—CASES OF CANCER OF THE PANCREAS.

Number of cases.	Percentage of fat in dried feces.	Percentage of nitrogen in dried feces.
1	72.8	8.0
2	61.3	5.8
3	52.0	4.5
4	52.0	2.0
5	63.3	3.0
6	36.3	1.7

There may be a relatively high content of nitrogen in the stools and yet the amount of dried stools be so small that the absorption of nitrogen may remain within normal limits. The dried feces of Miss S., a patient with ulcerative colitis, contained 5.6 per cent of nitrogen, but as the stools weighed only 74.5 gm., calculations showed that 91.6 per cent of the nitrogen of the food had been

absorbed. This is within the limits of normal as determined by v. Noorden,[27] who found that from 4 to 10 per cent of the nitrogen of a simple mixed diet fed to healthy persons could be recovered from the feces.

TABLE 4.—THREE-DAY TEST ON SCHMIDT DIET IN CASES OF STEATORRHEA.

Case.	Name.	Disease.	Weight of dried feces, gm.	Percentage of amount fed lost in feces.		
				Nitrogen.	Fat.	Carbohydrates.
9	Mr. B.	Steatorrhea of unknown origin	124	15.3	25.7	
10	Miss M.	Steatorrhea of unknown origin	130	11.1	11.8	1.6
11	Mrs. Ma.	Obstructive jaundice	131	7.0	18.8	
12	Mr. C.	Sprue	149	9.6	32.9	0.3
14	Mrs. D.	Obstructive jaundice complete	221	8.0	43.8	0.8
15	Mrs. W.	Sprue	269	13.2	45.1	0.5
16	Prof. G.	Obstruction of common and pancreatic ducts	419	47.7	65.5	0.8
17	Mr. Mc.	Complete obstruction of pancreatic ducts	438	50.9	58.9	0.8

Carbohydrate Absorption in Steatorrhea. The amount of carbohydrate in the stools has been determined by a method devised in our laboratory and found satisfactory.[28] In all the cases of steatorrhea studied by us, the starch of the diet has been very well utilized. The lowest percentage absorbed was 98.4—in other words, of the starch fed, only 1.6 per cent could be recovered from the dried feces. This was our case of obstruction of the pancreatic ducts with complete icterus. In sprue, 98.6 to 99.7 per cent of the starch of the food was absorbed. Gas bubbles often seen in the stools in cases of sprue cannot be attributed to the fermentation of starch, as practically no starch is present as our analysis shows. As these stools contain usually much of the fat in the form of soap, the suggestion of v. Noorden may be correct that the bubbles present are due to the foam-producing action of the soap present.

Summary. The fat content of the dried feces was determined in 33 cases. In 25 cases 30 or more per cent of fat was present. In 15 cases, 50 or more per cent of the dried feces was composed of fat. These instances of steatorrhea were due to obstructive jaundice, obstruction of the pancreatic ducts or sprue, except in 3 cases in which the cause of the fatty diarrhea was not discovered.

The absorption of fat was studied in 16 cases, using the standard intestinal test diet of Adolf Schmidt. The fat lost in the feces ranged from 2.1 per cent in the case of a patient with normal digestion to 66.2 per cent in a man with obstruction of the common bile duct and the pancreatic ducts. In the cases of steatorrhea, with two exceptions, 24 per cent or more of the fat of the food was excreted in the feces.

The absorption of the nitrogen of the test diet was determined in this group of 16 cases. In obstruction of the pancreatic ducts there was a loss of nitrogen in the stools, indicating faulty digestion and absorption of protein. When fat loss was due to absence of bile from the intestine the absorption of nitrogen remained normal. In sprue, the absorption of nitrogen is usually normal, but may be disturbed.

The utilization of the starch in the food was normal in all the cases of steatorrhea studied.

The chemical analysis of the feces for fat is important in determining, even approximately, the fat content of the stools as the results of the microscopic examination of the fresh feces may be misleading.

The determination of the percentage of nitrogen in the feces has proved of no value in diagnosis.

To study adequately cases of fatty diarrhea it is necessary to determine the absorption of both nitrogen and fat with the patient on a weighed diet, preferably the standard intestinal test diet of Schmidt.

Excluding the cases of steatorrhea due to absence of bile from the intestine, most of the cases studied in the present series have proved to be sprue or pancreatic disease.

In this study 3 cases of steatorrhea of unknown origin have been encountered. Further work is needed on similar cases. This should include in addition to the clinical study a complete quantitative chemical analysis of the feces for the remains of food elements and the determination of the amount of fat and nitrogen of the food that is lost in the stools, and finally a thorough study of the abdominal organs at autopsy.

REFERENCES.

1. Katz, A.: Wien. med. Wchnschr., 1899, **49**, 153.
2. Schmidt, A.: Schmidt and Strasburger, Die Fäzes des Menschen, 4th ed., Berlin, 1915, p. 178.
3. Müller, F.: Virchow's Arch. f. path. Anat., 1893, **131**, 18.
4. Hill, E., and Bloor, W. R.: J. Biol. Chem., 1922, **53**, 171.
5. Northrup, W. P., and Herter, C. A.: Am. J. Med. Sci., 1899, **117**, 131.
6. Müller, F.: Ztschr. f. klin. Med., 1887, **12**, 45.
7. Abelmann, M.: Inaug. Dissert., Dorpat, 1890.
8. Pratt, J. H., Lamson, P. D., and Marks, H. K.: Trans. Assn. Am. Phys., 1909, **24**, 266.
9. Zoja, G.: Morgagni, 1899; Abstract, Centralbl. f. inn. Med., 1899, **20**, 1261.
10. Tileston, W.: Arch. Int. Med., 1912, **9**, 525.
11. Deucher, P.: Korrespondenzbl. f. Schweiz. Aerzte, 1898, **28**, 321, 361.
12. Ehrmann, R.: Ztschr. f. klin. Med., 1910, **69**, 319.
13. Brugsch, T.: Ibid., 1906, **58**, 518.
14. Harley, V., and Goodbody, F. W.: The Chemical Investigation of Gastric and Intestinal Diseases by the Aid of Test Meals, London, 1906, p. 96.
15. Lohrisch, H.: Deutsch. Arch. f. klin. Med., 1904, **79**, 383.
16. Tomaszewski, Z.: Med. Klin., 1909, **5**, 439.
17. Schmidt, A.: Verhandl. d. Kong. f. inn. Med., 1895, **13**, 320.
18. Wendt, H.: Ergebn. d. inn. Med. u. Kinderh., 1932, **42**, 246.
19. Gutzeit, K., and Wendt, H.: Deutsch. Arch. f. klin. Med., 1930, **168**, 312.

20. Von Noorden, C., and Isaac, S.: Die Zuckerkrankheit und ihre Behandlung, 8th ed., Berlin, 1927, p. 286.
21. Hill, E., and Bloor, W. R.: J. Biol. Chem., 1922, **53**, 171.
22. Cited by Strasburger, J.: v. Mohr and Staehelin, Handb. d. inn. Med. 2d ed., Berlin, 1926, **3**, 489. See also Van der Scheer, Handb. der Tropenkrankh., 2d ed., Leipsic, 1914, **3**, 485.
23. Pratt, J. H., and Hatch, R.: Boston Med. and Surg. J., 1908, **158**, 686.
24. Schmidt, A.: Zentralbl. f. inn. Med., 1916, **37**, 51.
25. Von Noorden, C., and Schmidt, A.: Klinik der Darmkrankheiten, 2d ed., Munich, 1921, p. 312.
26. Rubner, M.: Ztschr. f. Biol., 1879, **15**, 159.
27. Von Noorden, C.: Lehrbuch der Pathologie des Stoffwechsels, Berlin, 1893, p. 39.
28. Pratt, J. H.: Internat. Clin., 1931, **3**, 173.

TULAREMIA TREATED BY A NEW SPECIFIC ANTISERUM.

By Lee Foshay, M.D.,
Associate Professor of Research Bacteriology, University of Cincinnati, School of Medicine, Cincinnati, Ohio.

(From the Christ Hospital Institute for Medical Research and the Department of Bacteriology and Hygiene, University of Cincinnati.)

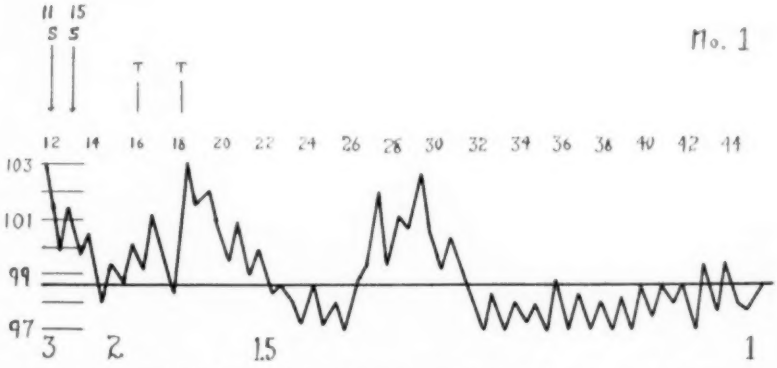
It is odd that tularemia, although known as a disease of man for 18 years, should have thus far escaped the usual trials for a specific treatment. A review of the literature reveals no reports of such attempts and the recent gratifying results obtained with the first trial antiserum make it seem improbable that this possibility has been tried before. The disease was first recognized as a human infection in 1914 by Wherry[1] in Vail's case of conjunctivitis,[2] the first proven case of tularemia. We are also indebted to Wherry and Lamb[3] for the discovery of our chief source of human infection in the eastern United States, namely the natural infection among wild rabbits. Also it may not be amiss to recall that the first note of warning concerning the real menace of widespread rodent tularemia to the health and safety of man came from the same source.[4] The incidence of diagnosed tularemia in man in this country has steadily and greatly increased since the publication of the many important researches carried out by Francis and his associates. These are too well known to need specific reference here. The disease has a rather low mortality rate, probably 4 to 5 per cent in this country, but its average duration is long and its victims are incapacitated for work for so many months that it has become a problem of considerable social and economic importance in this locality.

Since November, 1931, 15 tularemic patients have been treated with a specific antiserum prepared from a vaccinated goat. The method of production of the serum and the results of its experimental use in laboratory animals will eventually be reported elsewhere.

I wish to outline here the clinical results of its initial therapeutic trial. Although it is planned to continue these studies, the evidences for clinical value of the serum have been so striking that an amplified report of the preliminary announcement of this first year's experience seems justified, even though the number of cases is small.[5] No attempt has been made to concentrate or purify the goat serum. Most of it was used within a very short time after separation from the clot, but 4 patients were treated with serum that had been preserved and refrigerated for several months without apparent loss of potency. The time of illness at which patients were treated ranged from the 12th to the 77th day of disease. In most instances the serum was given by vein and the effectiveness of the small amounts that were used seems to indicate a fairly high degree of potency. With the exception of the fourth patient, who was admitted in a dying condition, the maximum amount of serum given to any 1 patient was 26 cc. Seven patients received a single dose each, in amounts of 5.5 to 17 cc. The experience is too limited to warrant any recommendations for dosage. One patient, a boy, aged 6, had the oculoglandular type of disease; all others had the usual ulceroglandular type with primary lesions on the fingers or hands. In every instance infection resulted from contact with wild rabbits and all diagnoses were confirmed by agglutination or intradermal tests and, wherever possible, by both tests. Further experience with the intradermal reaction as a diagnostic test gives results wholly confirmatory of those previously reported.[6]

The beneficial effects of the serum appear very soon after administration. Within 24 hours there is usually complete relief from headache and a marked diminution in intensity of general malaise, arthralgias and myalgias. Painful ulcers become much less distressing and epithelialization of their margins is usually well under way before the end of a week. The most pronounced evidences of curative action are the effects on temperature and on the enlarged lymph nodes. As indicated in the charts, there usually occurs a prompt fall in temperature and an amazingly rapid reduction in the diameters of the painful, tender, swollen lymph nodes. As the masses shrink in size they become less painful and less tender and often itch during this stage. In most instances this rapid reduction in volume has been permanent and suppuration has not occurred. In the two exceptions noted hereafter the nodes became smaller and painless but suffered a late secondary enlargement with liquefaction. Previously incised suppurating nodes show a marked diminution in the amount of drainage and a pronounced acceleration in healing. When dermal lymphangitic nodules and exanthematous lesions are present they usually disappear within a week. A fall in the leukocyte count accompanies these changes. These observations show the general trend of events. A few details and certain exceptions are noted in the following condensed abstracts of the case histories.

Case Abstracts. Case 1.—Ulcer on thumb, mass in left axilla, diffuse bronchopneumonia with dry pleurisy on left and effusion on right; severely ill. Good therapeutic response to serum. Skin test negative 3 days after second dose of serum. Unwisely given a skin test with very dilute heat-killed avirulent strain suspension, followed in 20 hours by pyrexia, 2 hemoptyses, marked extension of pleural and pulmonary signs and violent local inflammation resulting in necrosis and sloughing. Discharged after 33 days with one very small node in axilla, but apparently well. Returned in a month with a large left axillary abscess. By cultures and animal inoculations recovered streptococci and pneumococci; no P. tularensis. Well 11 days after incision of abscess. Disabled for 6 weeks. Duration of disease 2.3 months.



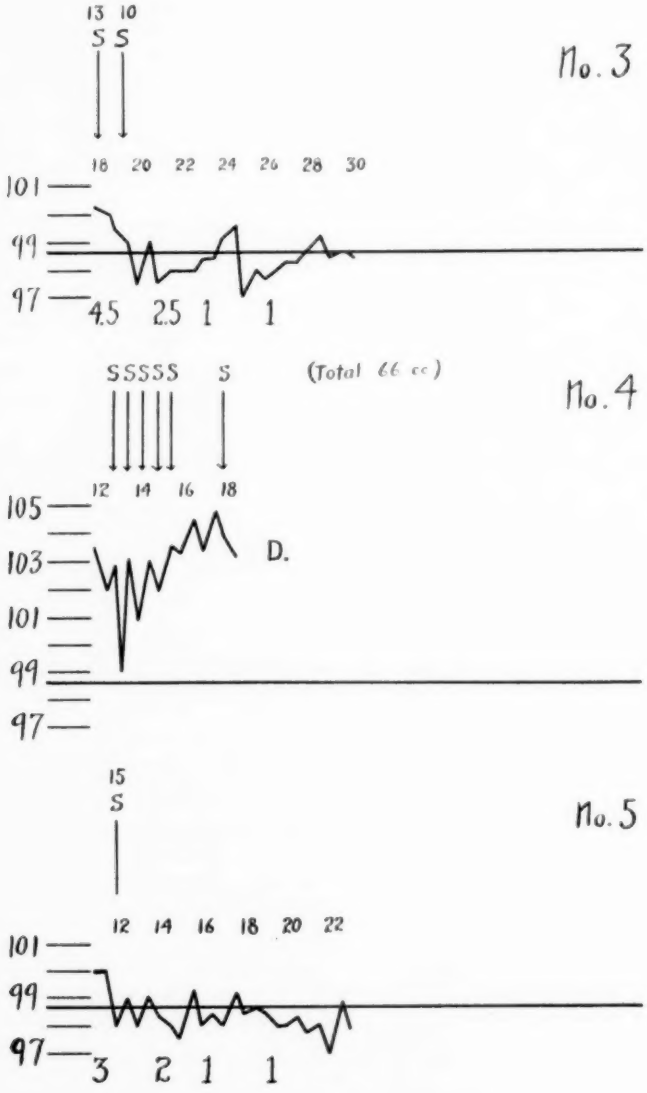
Maximum and minimum daily temperatures of the febrile patients treated in Cincinnati. Arrows surmounted by S show the time of injection and amounts of antiserum. Those surmounted by T indicate intradermal tests, and those under R indicate the time of onset of serum sickness. The horizontal row of figures immediately beneath the arrows indicates days of disease. The numerals at the bases refer to the diameters in centimeters of the involved lymph nodes. All temperatures were by mouth except those of Case 6, which were rectal.

Case 2.—Mild infection with ulcer on finger, nodular lymphangitis up left arm and large epitrochlear and axillary nodes. Afebrile but has drenching night sweats. Four days after serum the lymphangitic nodules were gone, sweats had stopped, nodes were ⅓ their former sizes and ulcer was dry, clean, painless and about ⅓ epithelialized. Discharged after 10 days with ulcer healed, nodes very small, skin test negative and without symptoms. Able to hunt rabbits 2d day after discharge. Last node impalpable at 3 months from onset. Disabled for 5 weeks. Duration of illness 3 months.

Case 3.—Painful ulcer on finger and palm and large mass in axilla. Severely ill with repeated chills, sweats and constant fever. Four days after serum the mass was half its former size, the ulcer painless, clean and about one-third epithelialized. Intradermal test moderately positive. Discharged after 13 days with one node just barely palpable. Returned 5 months after onset with an axillary abscess. Pus sterile to cultivation and animal inoculation. Wound healed 20 days after incision. Unable to work for only 1 month. Adenopathy lasted 5.5 months; duration of illness 6 months.

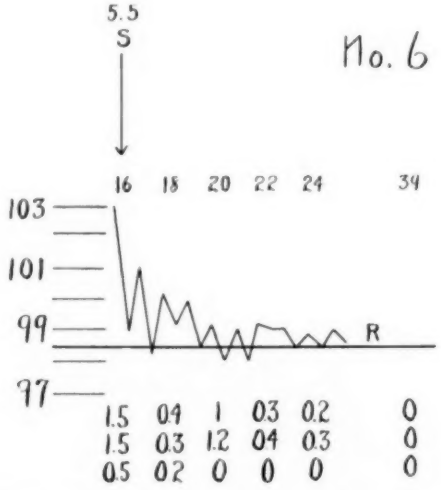
Case 4.—Admitted in dying condition; semicomatose, delirious, incontinent, with persistent hiccough and liver and spleen felt 6 cm. below costal margins. Except for one brief fall in temperature, accompanied by transient mental clarity, serum in large amounts was ineffective. Died on 6th hospital day. Necropsy not permitted.

CASE 5.—Daughter-in-law of preceding patient, infected from same rabbits. Multiple ulcers on both hands, moderately febrile, persistent chills, sweats and profound malaise; severe headache and substernal pain. Bilateral epitrochlear adenopathy. Four days after serum temperature



was normal, nodes ⅓ their former sizes, primary lesions painless and healing well. Skin test negative. Discharged after 12 days. All nodes impalpable 36 days after onset. Remained well. Resumed work 42 days after infection. Duration of illness 1.4 months.

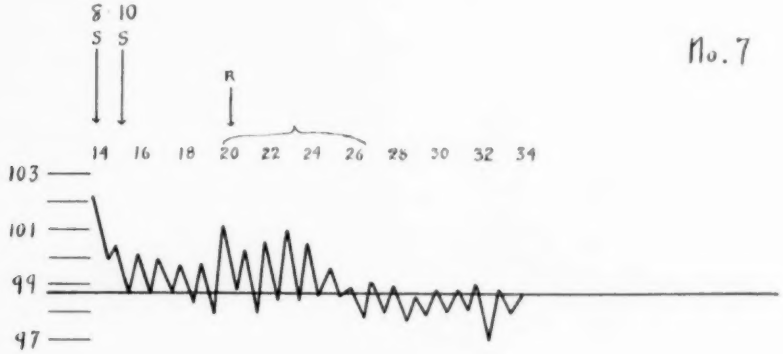
CASE 6.—Small boy with moderately severe right ocular infection and enlarged preauricular, anterior cervical and submaxillary nodes. Fever, sweats and ulcerations of palpebral conjunctivæ; marked chemosis of the globus and intense edema of lids. Papulovesicular exanthem on face, neck, scalp, forearms and hands. Four days after serum he was afebrile, nodes were ⅓ their former sizes, eye was perfectly clear, lids entirely healed and free from edema; exanthem gone. Discharged after 10 days entirely well and has remained so. Duration of adenopathy 19 days; out of kindergarten 1 month; total duration of disease 41 days. Slight enophthalmos of the right eye is still noted 15 months after the onset.

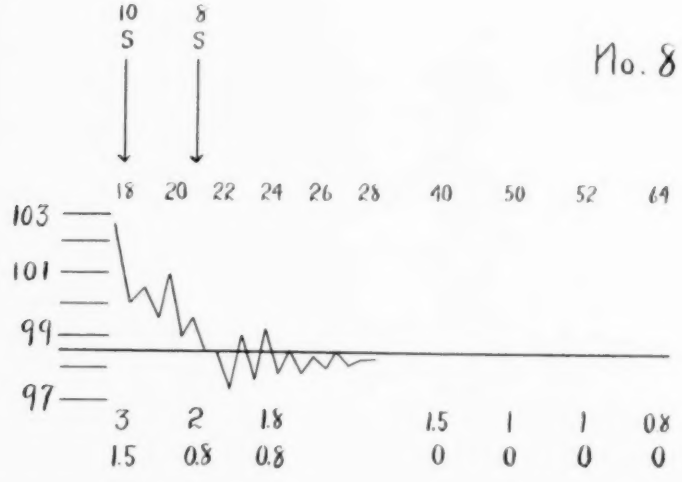


CASE 7.—Typical onset with sore on thumb, fever, chills, sweats, malaise and a bubo in the right axilla. Adenopathy was transient and had entirely disappeared by the time serum was given. On the 13th day of illness an extensive exanthem appeared, which became maximal in size and distribution 2 days later, 1 day before the accompanying photographs were taken. The distribution is exactly as shown, including scalp lesions. There is a striking similarity between this exanthem and the maximal allergic response to an excessively large intradermal test. Four days after serum temperature was almost normal, headache had disappeared, also the chills, sweats and malaise. The skin lesions were about one-third involuted, almost flat and less intensely colored. They never itched. The patient, a known allergic person, had at this point moderately severe serum sickness with generalized urticaria, fever for a week, malaise, headache and intensification of the skin lesions. It was 4 months before the last traces of the exanthem had disappeared. Although no lymph nodes had been felt since the 10th day of disease, there occurred suddenly, 3 months after the onset, a painless axillary enlargement which fluctuated in size for the next 4 months, gradually getting larger until it ruptured. The sinus healed in 11 days. The patient has remained well but still gives positive skin tests a year after infection.

CASE 8.—Mother of the small boy and infected from the same rabbit. Severely ill; usual symptoms and early course. Four days after serum she was afebrile, comfortable and buboes were half their former sizes. Intradermal test very slightly positive. Convalescence was uneventful. She was disabled for 40 days. Adenopathy lasted for 2.6 months but she was otherwise well and active 2 months after onset.

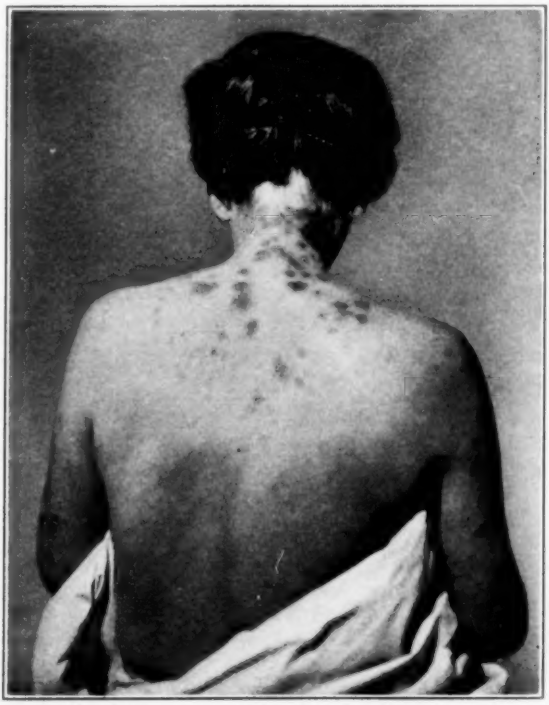
CASE 9.—Typical ulceroglandular onset and course. Nodes very large and painful but malaise mild since the end of the 2d week. Seen on the 28th day of disease and treated as an ambulatory case. After 3 days the nodes were half their former size and the residual general symptoms were gone. The nodes subsided slowly, disappearing after 3 months, although she felt well at 2.5 months and had been disabled for 1 month.





CASE 10.—Severe ulceroglandular type with epitrochlear and axillary adenitis; elderly man. Seven days after serum he was afebrile and nodes were reduced one-third. Headache and malaise disappeared on the 3d day. The last node disappeared in 30 days and he was well 2 months from onset with a negative intradermal test.

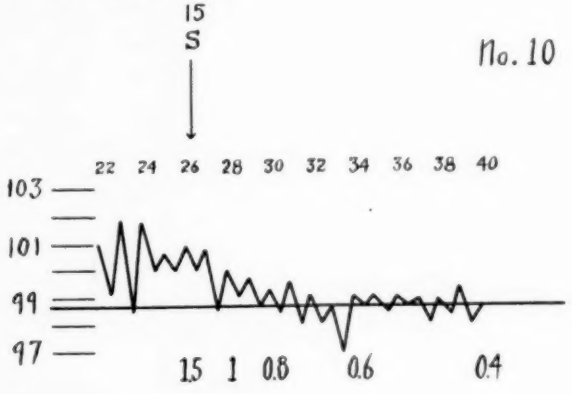
CASE 11.—Ulcer on finger, high fever, headache, chills, sweats, cough, malaise and a large painful lump in the left axilla. Four days after serum she felt well, was less febrile and the mass was diminished by more than half. Convalescence was delayed by serum sickness which caused 7 days of fever and 4 days of urticaria; also by failure to maintain wet dressings on the ulcer with consequent secondary infection. Adenopathy disappeared 42

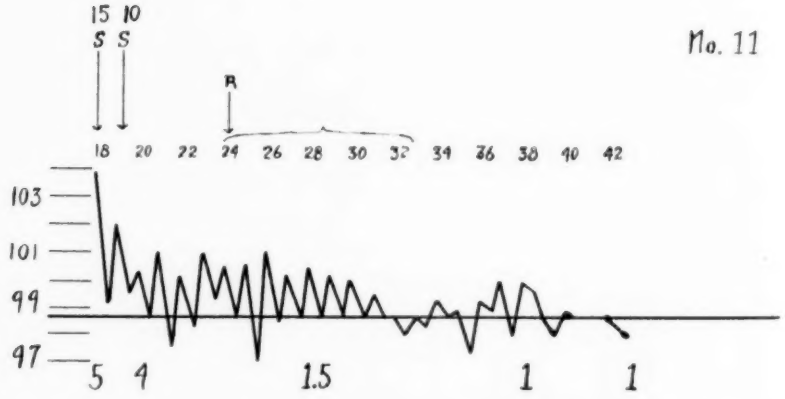


The maculo-papulo-vesicular exanthem of Patient 7. The photographs were taken 1 day after the rash had reached its maximal spread and intensity. The healed primary lesion is visible on the tip of the right thumb.

days after onset. She was disabled for 6 weeks and completely well after 2 months, when a skin test was negative.

CASE 12.—Severe infection with multiple primary lesions, cellulitis of hand and arm, then multiple abscesses of hand, forearm and axilla requiring drainage and irrigation. Serum given on the 77th day of disease. Patient constantly febrile. Two days after serum he became afebrile; no more nodes suppurated and the old incisions healed rapidly. He was well 3 months after the onset.





CASE 13.—Multiple primary lesions, fever, chills, sweats and adenopathy involving axillary, epitrochlear and supraclavicular nodes. Papulovesicular exanthem on face, neck and upper thorax. Few subdermal lymphangitic nodules along right forearm. Five days after serum the nodes were ⅓ their former sizes, painless, and the exanthem and nodules had disappeared. Urticaria occurred 7 days after serum and lasted 2 days. Three weeks after serum all nodes were impalpable, ulcers were healed and she was well and has remained so. Skin test negative.

CASE 14.—Infected by skinning a rabbit caught by his dog. Multiple ulcers, sore throat, fever, chills, sweats, profound malaise and axillary adenitis which suppurated and was incised. Drainage continued unchanged for 2 weeks, with no sign of healing. Five days after serum the axilla was painless and healing had begun. The serum caused a moderately severe

immediate reaction with a chill and fever which lasted 2 days. Two weeks after serum he was well. Total duration of illness was 3 months.

CASE 15.—Wife of preceding patient and infected by the same rabbit. Headache, severe malaise, fever, chills, pain in forearm, multiple ulcers on hand, extensive cellulitis of forearm and arm, and painful axillary bubo. An axillary abscess had formed before serum was given. It was incised on the 6th day after serum when the temperature fell to normal and all symptoms disappeared. The incision healed in 2 days and she has remained well since. Adenopathy lasted for 10 weeks and the duration of disease was 81 days.

Comment. It seems clear that the clinical course of tularemia is susceptible to favorable modification by specific therapy. Although the serum was useful even in the 2d and 3d months of disease, it seems best to give it as early as possible in order to prevent glandular suppuration and also with the aim of preventing deaths from the septicemic form. When infection was limited to the skin, lymphatic structures and respiratory apparatus good recoveries followed serum injection. If the liver and spleen have become infiltrated it is then probably too late to expect the serum to be of any use. No correlation was observed between the agglutinin titers, ranging from 1 to 80 to 1 to 1280, and its clinical effectiveness.

It is clearly shown by the results of the intradermal tests that the therapeutic properties of this antiserum are closely linked with its desensitizing action. All but 2 of the patients who could be reached for subsequent skin testing were shown to be either wholly or almost completely desensitized by the serum injections. The two exceptions were the 2 patients in whom delayed secondary glandular enlargements recurred months after the initial buboes had disappeared. A possible explanation of this may be that the failure to induce desensitization means inadequate serum therapy. Indeed it may be that the prompt and permanent therapeutic effects noted in the other patients have been made possible by the rapidity and completeness with which desensitization had been induced, the opinion now held to account for the serum's action. This is supported by observations reported elsewhere[6] where it was shown that small daily injections of suitable *P. tularensis* suspensions could induce the identical rapid curative action that has been noted in the serum-treated patients. In the vaccine-treated patients it had been determined that the abrupt disappearance of signs of the disease was sharply coincident with the establishment of desensitization. This is a particularly striking and dramatic phenomenon in tularemia because of the extreme hypersensitivity manifested by all patients to very minute amounts of diluted antigens. Furthermore, in untreated patients this state of hypersensitivity continues without detectable diminution for at least 15 months. Clinical experience with tularemia up to the present time indicates that the removal or abolition of the state of bacterial hypersensitivity either by vaccination or by serum injection is a *sine qua non* for rapid recovery.

TABLE 1.—RESULTS OF SERUM TREATMENT IN 15 CASES.

Case No.	Sex.	Age.	Treatment begun; day of disease.	Total serum in cc.	Doses given.	Diameter of lymph nodes in cm.		Skin test after serum.	Duration of disease (days).
						Before serum.	4 days later.		
1	M.	40	12	26.0	2	2.5	1.0 (S)	Neg.	70
2	M.	36	21	13.0	2	3.0	1.0	Neg.	90
3	F.	37	18	23.0	2	4.5	2.5 (S)	Pos.	180
4	M.	67	12	66.0	6	4.0	2.0	....	18 (Died)
5	F.	32	12	15.0	1	3.0	1.0	Neg.	42
6	M.	6	16	5.5	1	1.5	0.4	Neg.	39
7	F.	47	14	18.0	2	...	... (S)	Pos.	240
8	F.	27	18	18.0	2	3.0	2.0	Neg.	60
9	F.	35	27	15.0	2	4.0	2.0	....	75
10	M.	71	22	15.0	1	1.5	1.0	Neg.	51
11	F.	38	18	25.0	2	5.0	3.0	Neg.	60
12	M.	20	77	13.0	1	...	... (I)	....	90
13	F.	45	46	8.0	1	5.0	3.0	Neg.	67
14	M.	41	72	17.0	1	...	... (I)	....	90
15	F.	33	72	17.0	1	6.0	4.0 (I)	....	81

In the column giving diameters of nodes after treatment the letters in parenthesis indicate suppuration. S indicates suppuration after treatment and I indicates suppuration and incision before treatment.

In addition, all experience to date indicates that the antiserum is neither bacteriostatic nor bactericidal, and that it is not protective for rodents even when they are treated a day in advance of dermal infection. For example, 10 cc., an amount sufficient to induce a prompt recovery in a 70 kg. man, will not prevent death in a 1.3 kg. rabbit. Hence the chief attribute that at present can be correlated with its beneficial action in man is its capacity to induce specific desensitization. It was somewhat astonishing to see the rapid clinical recoveries that followed single small doses in Cases 5, 6, 10, 14 and 15. These responses to such small doses must be considered in any explanation of the mode of action.

TABLE 2.—COMPARATIVE DATA FROM CONTROL AND SERUM-TREATED CASES.

Duration of:	Average in days.	
	Control cases (1930–1931)	Treated cases (1931–1932)
Fever	35	21
Hospitalization	30	15
Lymphadenopathy	115	66
Disability	141	51
Disease	165	88

The control data come from the last 16 patients admitted to the hospital before serum treatment was instituted. Febrile days due to serum sickness are included in the average for the treated cases. Serum therapy secured distinct advantages, both clinical and economic, for the treated group.

It is noteworthy that there was no acute suppuration of any enlarged lymph nodes except in the axillary bubo of the first case, where there is some reason to believe that the secondary invad-

ing organisms contributed to the liquefaction. I believe that early diagnosis and treatment may diminish the incidence of suppurative adenitis. Late recurrent glandular suppurations, seen in Cases 3 and 7, have been observed previously in untreated tularemia, some occurring after 5 or 6 months of apparent well being. It would seem that necrosis in the nodes had progressed so far by the time natural or induced apparent recovery took place that the resultant products were not absorbable. The cold abscesses thus formed dissected slowly towards the surface and their pus was sterile both to cultivation and animal inoculation.

In regard to the technique of intradermal tests, it is very important not to use heat-killed antigens. Grave consequences, both focal and constitutional, may result. A reliable and safe suspension has been made and standardized for this purpose. Before the 8th day of disease a skin wheal $\frac{1}{4}$ inch in diameter is made with it. Later in the disease a wheal half this size is sufficient. Constantly reliable and satisfactory reactions have been obtained in this way. The bacteria are detoxified by nascent nitrous acid. Exactly 5 cc. of a formaldehyde-killed suspension of turbidity 5000 are cleared by centrifuging and the bacteria resuspended in 4 cc. of freshly prepared 30 per cent sodium nitrite. Then 4 cc. of 30 per cent acetic acid are added. This mixture is stood at room temperature for about 20 hours, when the bacteria are thoroughly washed and ultimately restored to a final volume of 10 cc., making a stock suspension of turbidity 2500. A diluted suspension for intradermal tests is made by adding 0.30 cc. of this stock to 15 cc. of saline containing a suitable preservative, the final suspension having a turbidity of 50 against the Fuller's earth standard.

Summary. An initial trial has shown that the goat can be made to yield a potent antitularense serum which is effective in treating tularemia in man. The intravenous administration of this serum produced a marked and prompt amelioration of symptoms in 14 out of 15 tularemia patients and caused a shortening of the duration of adenopathy, the period of disability and the total duration of disease. One patient, received in dying condition with extensive involvement of the lungs, liver and spleen, was not improved. The antiserum has a specific desensitizing action. There is evidence to show that its beneficial effects in man are intimately associated with, and perhaps dependent upon, this property.

REFERENCES.

1. Wherry, W. B., and Lamb, B. H.: Infection of Man with Bacterium Tularense, J. Infect. Dis., 1914, **15**, 331.

2. Vail, D. T., Sr.: A Case of "Squirrel Plague" Conjunctivitis in Man: Bacillus Tularense Infection of the Eye, Ophthal. Rec., 1914, **23**, 487.

3. Wherry, W. B., and Lamb, B. H.: Discovery of Bacterium Tularense in Wild Rabbits and the Danger of Its Transfer to Man, J. Am. Med. Assn., 1914, **63**, 2041.

4. Wherry, W. B.: A New Bacterial Disease of Rodents Transmissible to Man, Pub. Health Rep., No. 51, 1914, **29**, 3387.

5. Foshay, L.: Serum Treatment of Tularemia, J. Am. Med. Assn., 1932, **98**, 552.

6. Foshay, L.: Tularemia: Accurate and Earlier Diagnosis by Means of the Intradermal Reaction, J. Infect. Dis., 1932, **51**, 286.

THE RÔLE OF INFECTION IN GASTRIC AND DUODENAL ULCER.*

By Edward Watts Saunders, M.D., F.A.C.S.,
INSTRUCTOR IN SURGERY, ASSOCIATE IN SURGICAL RESEARCH, CORNELL UNIVERSITY MEDICAL COLLEGE; ASSISTANT ATTENDING SURGEON, SECOND SURGICAL DIVISION (CORNELL), BELLEVUE HOSPITAL,

Hubert B. Holsinger, M.D.,
ASSISTANT IN SURGICAL RESEARCH, CORNELL UNIVERSITY MEDICAL COLLEGE,

AND

Mary A. Cooper, B.S.,
ASSISTANT IN SURGICAL RESEARCH, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK, N. Y.

(From the Department of Surgical Research, Cornell University Medical College.)

This work involves the isolation of a streptococcus from 30 resected ulcers of the stomach and duodenum by planting bits of the ulcer tissue in 0.5 per cent hormone agar immediately upon resection; the proving of all these strains identical by agglutination, cross agglutination, and agglutinin absorption; proving the organism identical with three strains isolated from cow's milk; and in previous work proving its non-relationship to all other focus streptococci tested.[6–9]

Its further relationship to ulcer has been previously shown by the high titer agglutination of patient's sera suffering from gastric ulcer against an antigen of this organism, and the non-agglutination of control sera.

It has been demonstrated to be present in great numbers in immediately prepared Levaditi sections of human ulcers.

With these facts apparent, the following experimental work was undertaken to determine the rôle played by this organism in the production of ulcers. The following tables record the results and are self-explanatory. The operation of surgical duodenal drainage was identical with that devised by Mann and Williamson[1]. Culture 105 was used for feeding the 10 test dogs.

Fourteen ulcers were present in 5 of the group of 10 dogs fed the organism, while only 2 were present in the control group of 9 dogs.

The photographs demonstrate quite well the difference between the infected ulcer and the non-infected ulcer. If one compares them with a typical human ulcer, and follows the criterion of Askanazy,[2] that there are 4 typical zones present, (1) exudation, (2) fibrinoid necrosis, (3) granulation, and (4) cicatrization, then the infected ulcers are the only ones comparable to those found in man, and the others merely erosions. Sections were made of every ulcer, and the difference noted above was similar in each case.

* This report was aided by a gift from Mrs. John L. Given in support of Surgical Research.

TABLE 1.—CULTURAL AND SEROLOGICAL RELATIONSHIP OF ALL STRAINS.

Culture.	Source.	Hemolysis of blood.	Agglutination with sera 2, 66 and 83, titer 2 1–12800, 66 1–6400, 83 1–6400	Agglutination after absorption with sera 2, 66 and 83.	Fermentation reaction. Esculin bile.	Sodium thiosulphate media; degree of blackening by sulphur production.	Acidity figure; change of 1 per cent glucose broth from pH 7.4 to.	Mannite fermentation.	Heat resistance; growth on 1 per cent lactose agar after heating at 63° for 45 min.	Lactose fermentation in 24 hours.
46	Duodenal ulcer	A	1–12800	0	+	+	4.3	+	+	+
64	Duodenal ulcer	A′	1–6400	0	+	+++	4.4	+	+	+
67	Duodenal ulcer	A′	1–6400	Trace 1–100						
55	Gastrojejunal ulcer	A	1–12800	0	+	+	4.5	+	+	+
56	Gastrojejunal ulcer	A	1–12800	0	+	++	4.6	+	+	+
2	Gastric ulcer	A	1–12800	0	+	++	4.4	+	+	+
19	Gastric ulcer	A′	1–12800	0	+	+	4.5	+	+	+
20	Gastric ulcer	A′	1–12800	0	+	+	4.6	+	+	+
23	Gastric ulcer	A	1–12800	0	+	++	4.4	+	+	+
47	Gastric ulcer	A	1–12800	0	−	+	4.5	−	+	−
53	Gastric ulcer	A′	1–12800	0	+	+	4.6	−	+	+
58	Gastric ulcer	A′	1–6400	0	+	++	4.3	+	+	+
61	Gastric ulcer	A′	1–6400	0	+	++++	4.3	+	+	+
62	Gastric ulcer	A′	1–12800	0	+	+++	4.4	+	+	+
63	Gastric ulcer	A′	1–6400	0						
68	Gastric ulcer	A′	1–6400	Trace 1–100	+	++	4.4	−	+	+
74	Gastric ulcer	A	1–3200	0	−	+	4.4	−	−	−
83 S	Gastric ulcer	A	1–3200	Trace 1–100	+	+	4.5	−	−	−
83 R	Gastric ulcer	A	1–3200	Trace 1–100	+	+++	4.4	+	+	+
104	Gastric ulcer	A	1–3200	Trace 1–100	+	+++	4.6	+	+	+
105	Gastric ulcer	A	1–3200	Trace 1–100	+	+++	4.6	+	+	+
9	Dog ulcer	A	1–6400	0	+	++	4.4	+	+	+
45	Gastric ulcer carcinoma	A′	1–12800	0	+	+	4.3	+	+	+
59	Gastric ulcer carcinoma	A′	1–12800	0	+	+	4.6	+	−	+
60	Gastric ulcer carcinoma	A′	1–12800	Trace 1–100	+	++	4.6	+	−	+
66	Gastric ulcer carcinoma	A′	1–6400	0	+	+++	4.4	+	+	+
79	Gastric ulcer carcinoma	A	1–3200	0	+	+	4.3	+	+	+
79 B	Blood stream, gastric ulcer carcinoma	—	1–3200	Trace 1–100	+	+	4.4	+	+	+
95	Gastric ulcer carcinoma	A	1–6400	0	+	+++	4.4	+	+	+
116	Gastric ulcer carcinoma	A	1–3200	Trace 1–100	+	+++	4.4	+	+	+
90	Cow's milk	A′	1–6400	Trace 1–100	−	+	4.6	−	+	+
91	Cow's milk	A′	1–6400	Trace 1–100	−	+	4.8	−	+	+
100	Cow's milk	A	1–6400	Trace 1–100	−	++	4.6	−	+	+

Note (1) Strains 63 and 67 lost before cultural work was completed.
(2) Cultures 2 through 58 agglutinated against serum 2.
Cultures 58 through 83 agglutinated against serum 66
Cultures 90 through 116 agglutinated against serum 83.

TABLE 2.—GROUP OF DOGS FED ULCER STREPTOCOCCUS.

Number.	Days fed organisms.	Lesions found.	Cause of death.
1	7	One ulcer	Killed because of distemper
2	17	One ulcer	Killed
3	79	No ulcers	Killed
4	36	No ulcers	Anaphylactoid shock
5	38	Five ulcers	Perforated ulcers
6	40	Four ulcers	Killed
7	28	Three ulcers	Killed
8	50	No ulcer	Killed
9	47	No ulcer	Killed
10	49	No ulcer	Killed

Average number of days organisms were fed, 39.
Percentage of ulcer formation, 50.

TABLE 3.—CONTROL GROUP OF DOGS.

Number.	Number of postoperative days.	Lesions found.	Cause of death.
1	30	No ulcer	Distemper
2	14	No ulcer	Distemper
3	47	One ulcer	Killed
4	27	No ulcer	Killed
5	40	One ulcer	Distemper
6	22	No ulcer	Distemper
7	43	No ulcer	Distemper
8	35	No ulcer	Killed
9	70	No ulcer	Reoperated

Average number of postoperative days, 36.
Percentage of ulcer formation, 22.

Discussion. Berg and Jobling,[3] in reporting their incidence of ulcer following double ligation of the common duct, noted 100 per cent incidence in those animals which were kept under unsanitary conditions, and only a 30 per cent incidence in those kept in sanitary quarters, and fed well prepared food.

Bollman and Mann[4] stated that there was a definite tendency for ulcers to form in animals following double ligation of the common duct, that is, several weeks would elapse without the death of a single animal from ulcer, and then several deaths might occur in the same week without reference to the duration of jaundice. They were unable to ascribe this periodicity to diet, hygienic conditions, or other known factors.

Infection is the only basis upon which these discrepancies can be explained.

The organism studied by us is found in milk from cows suffering with mastitis, and is not identical with any other type of streptococcus tested. It will stand the heat of pasteurization, it does not live in bile media of the lowest dilutions, and is not affected by a high acidity.

It is the only factor which can explain the epidemic-like occurrence of ulcer in children from 1 to 6 months of age as reported by Helmholz.[5]

Summary. An identical organism has been isolated from 30 resected ulcers of the stomach and duodenum, and has been proved identical with 3 others isolated from cow's milk, and is not identical with any other streptococcus tested.

Following surgical duodenal drainage in dogs, 14 typical ulcers were found in 5 of the group of 10 fed cultures of the organism, and only 2 erosions in 2 of the control group of 9 not fed the organisms.

REFERENCES.

1. Mann, F. C., and Williamson, C. S.: Ann. Surg., 1923, **77**, 409.
2. Askanazy, M.: Virch. Arch. f. path. Anat., 1924, **234**, 111; 1924, **250**, 370.
3. Berg, B. N., and Jobling, J. W.: Arch. Surg., 1930, **20**, 997.
4. Bollman, J. L., and Mann, F. C.: Ibid., 1932, **24**, 126.
5. Helmholz, H. F.: Arch. Pediat., 1909, **26**, 661.
6. Saunders, E. W.: Arch. Int. Med., 1930, **45**, 347.
7. Saunders, E. W.: Ann. Surg., 1930, **91**, 222.
8. Saunders, E. W.: Am. J. Cancer, 1931, **15**, 2745.
9. Saunders, E. W.: Ann. Surg., 1932, **95**, 327.

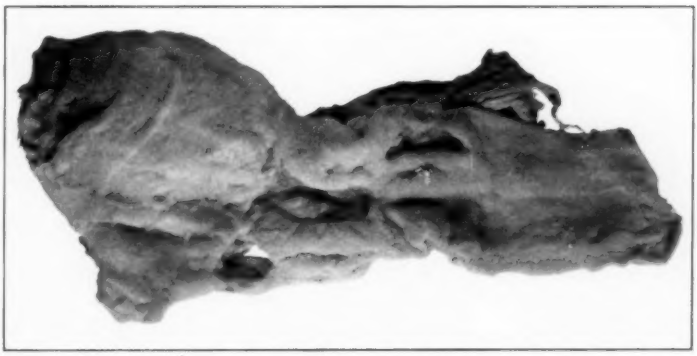


FIG. 1.—Gross picture, Dog 5, Table 2. The ulcer edges are sharply defined and overhanging. One of the ulcers at the site of anastomosis had perforated. Another shows evidence of having previously perforated, and having been sealed off with omentum.

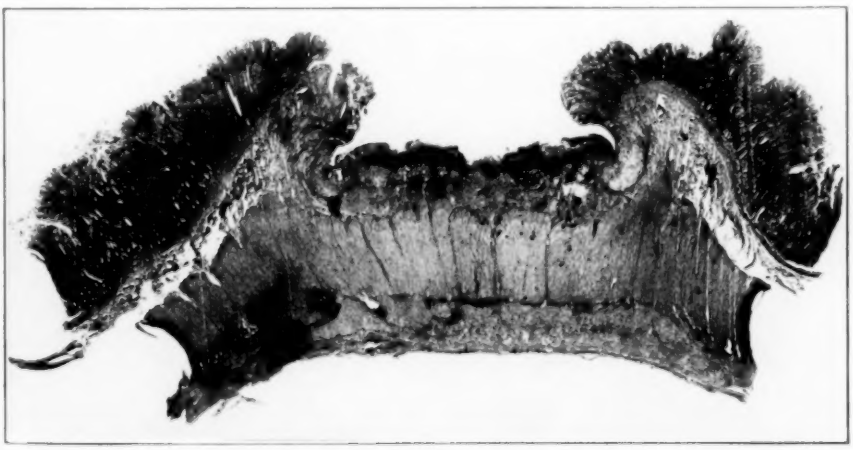


FIG. 2.—Full section of ulcer, Dog 5, Table 2. Showing overhanging edges and necrotic base. (Very low magnification.)

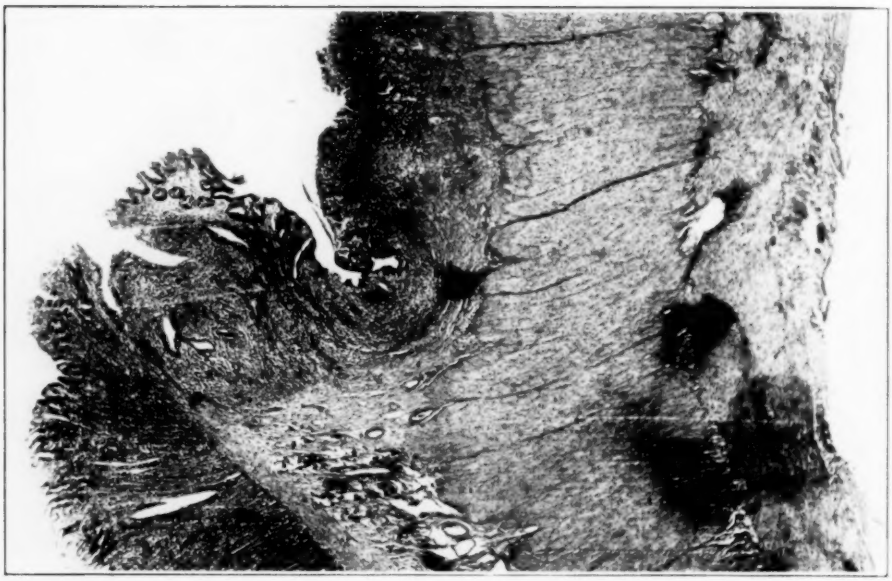


FIG. 3.—Low power through crater of ulcer from Dog 5, Table 2. Showing all four zones: exudation, necrosis, granulation, and cicatrization. Almost identical with human ulcer section.

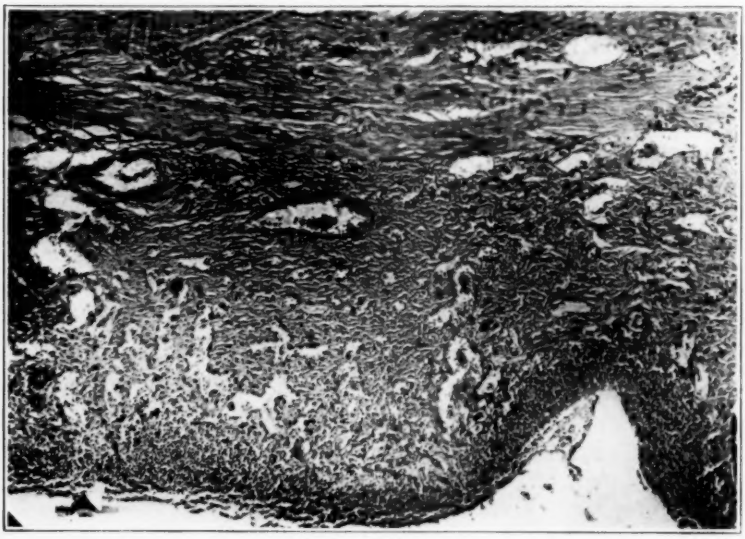


FIG. 4.—This is a section through ulcer crater of Dog 1, Table 2. It demonstrates beautifully the four zones: exudation, necrosis, granulation and cicatrization.

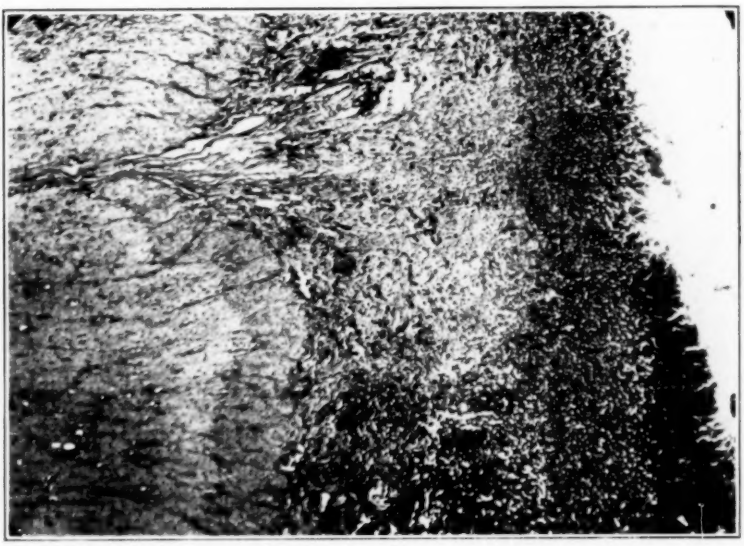


FIG. 5.—This is a section through a crater from a human ulcer. It demonstrates the four zones: exudation, necrosis, granulation, and cicatrization.

FIG. 6.—Gross picture of site of anastomosis of Dog 3, Control Group, Table 3. The ulcer is single. The edges are not overhanging.

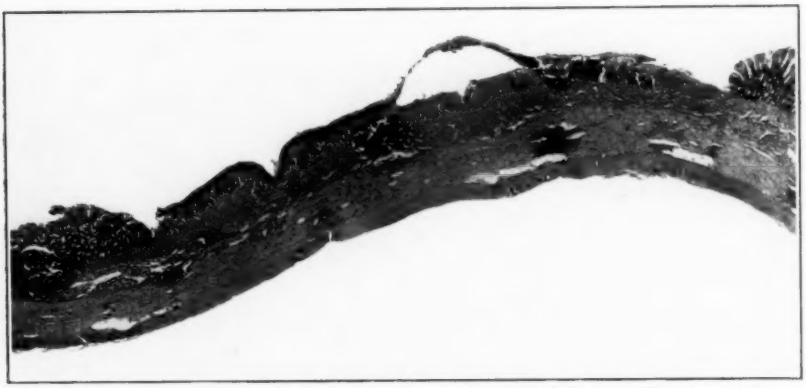


FIG. 7.—Ulcer, rather erosion, Dog 3, Control Group, Table 3. The four zones are not present. The stomach layers are intact.

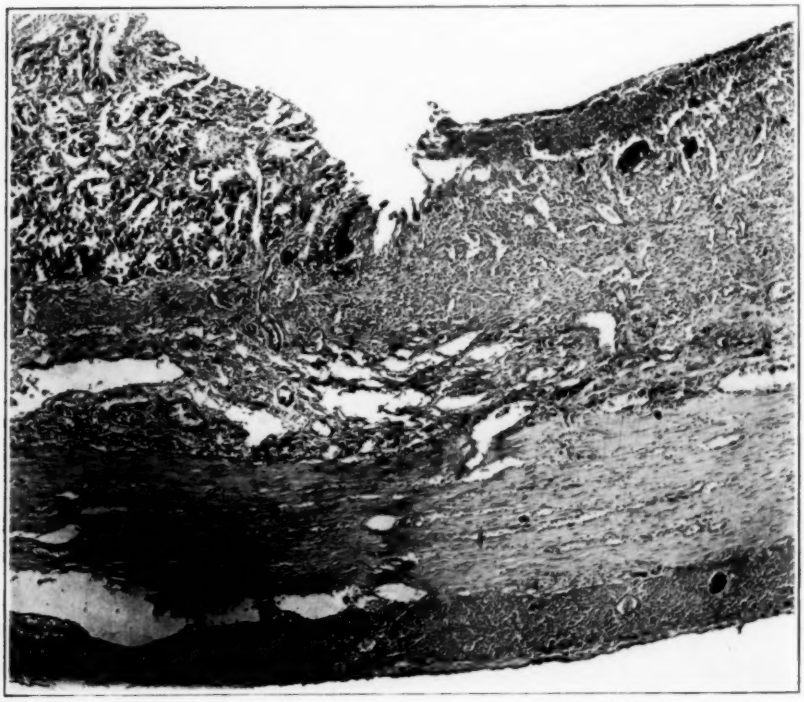


FIG. 8.—Low power section of ulcer, Dog 3, Control Group, Table 3. The four zones are not present.

ANAPHYLACTIC-LIKE REACTION PRODUCED BY THE STREPTOCOCCUS OF GASTRIC ULCER.*

By Edward Watts Saunders, M.D., F.A.C.S.,
INSTRUCTOR IN SURGERY, ASSOCIATE IN SURGICAL RESEARCH, CORNELL UNIVERSITY MEDICAL COLLEGE; ASSISTANT ATTENDING SURGEON, SECOND SURGICAL DIVISION (CORNELL), BELLEVUE HOSPITAL,

Hubert B. Holsinger, M.D.,
ASSISTANT IN SURGICAL RESEARCH,
AND
Mary A. Cooper, B.S.,
ASSISTANT IN SURGICAL RESEARCH, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK, N. Y.

(From the Department of Surgical Research, Cornell University Medical College.)

The purpose of this study was to determine the tissue reaction of animals to the streptococcus isolated from gastric ulcer. To study the reaction of the organism, it was first necessary to obtain it free from foreign material. Peptone produces shock when injected intravenously; therefore the organism was grown on a 1.05 per cent hormone agar slant, and particular care was used in preparing the slant in order to keep it free from foreign material. The organisms after growth were then collected by washing them off the slant with sterile normal saline.

The first studies were made on the reaction of skin and subcutaneous tissues. In intradermal injections in the dog there is no more reaction than one would get from injecting an equal amount of normal saline, except for the occasional development of a superficial ulcer. After 24 hours no evidence of reaction remained. In subcutaneous injections in the dog, again, there is no evidence of reaction after 24 hours. When the injected tissue was studied microscopically there were no changes found. In some of the dogs the skin and subcutaneous tissue were removed an hour after injection. In studying sections from these tissues the organisms were found lying free in the tissue spaces, and apparently some of them were intracellular, otherwise no tissue reaction was found. The most noticeable thing here was the absence of any type of extracellular infiltration.

In the rabbit there often developed at the site of the subcutaneous injection a well circumscribed, yellow caseous-like mass. Sections through this showed the caseous material to be composed of débris and a few small round cells. There was no reaction in the tissues immediately around the caseous material. In other words, the usual signs of inflammation were not present.

* This report was aided by a gift from Mrs. John L. Given in support of Surgical Research.

Next, threads infected with the organism were inserted in the wall of the stomach and duodenum, the thread passing through all three layers. The infected areas were removed at varying intervals from different dogs and studied microscopically. The sections failed to show tissue changes. Thyroids were treated in the same manner and here again there was an absence of any tissue change. The noticeable thing here, however, was the complete absence of extracellular infiltration, that is, there were no leukocytes, small round cells, or foreign body giant cells in the neighborhood of the infected thread. Ordinarily there is found around non-infected silk threads a slight extracellular infiltration and occasionally foreign body giant cells.

In one female dog in which the breasts were injected at weekly intervals for a 2½-month period, no changes were noted in the breasts except a slight increase in the fibrous tissue. The inguinal and axillary lymph nodes were markedly enlarged and a microscopic examination showed evidence of chronic inflammation.

Intravenous injections were next tried. Saline suspensions were used here as in the previous work. The first dogs injected were some that had previously been inoculated with the organism. In these dogs there developed either immediately, or within 2 hours after injection, a peculiar type of reaction, characterized by violent intestinal peristalsis as shown by intense spasm of the abdominal muscles, and frequent defecation and vomiting. One of these dogs died 4 hours later and another 24 hours later. At autopsy, the dog dying 4 hours after injection showed about 200 cc. of a hemorrhagic fluid in the peritoneal cavity, the liver presented a picture typical of hemorrhagic hepatitis, there were small hemorrhages in the wall of the gall bladder, and petechial hemorrhages in the mucosa of the stomach and duodenum. In the dog that died 22 hours after injection there was an absence of the intraperitoneal fluid, the same findings were present in the liver and gall bladder, except for more destruction of the central liver cells, and there was marked hemorrhage in the mucosa of the stomach limited to the cardia.

There were petechial hemorrhages in the visceral pleura of both lungs, and the lungs themselves presented atelectasis. One dog killed 20 minutes after injection showed only a hemorrhagic hepatitis. This type of reaction is known to be given by histamin, peptone, the toxin from high intestinal obstruction, and a similar type of reaction is produced by anaphylaxis from animal protein. Histamin was ruled out by extracting the suspension with 95 per cent alcohol and then evaporating the alcohol from the filtrate. The residue when taken up with saline gave no reaction. The precipitate from the alcoholic extract gave the reaction. Also histamin was ruled out physiologically by the guinea-pig test. Peptone was ruled out by taking the saline washings from a number

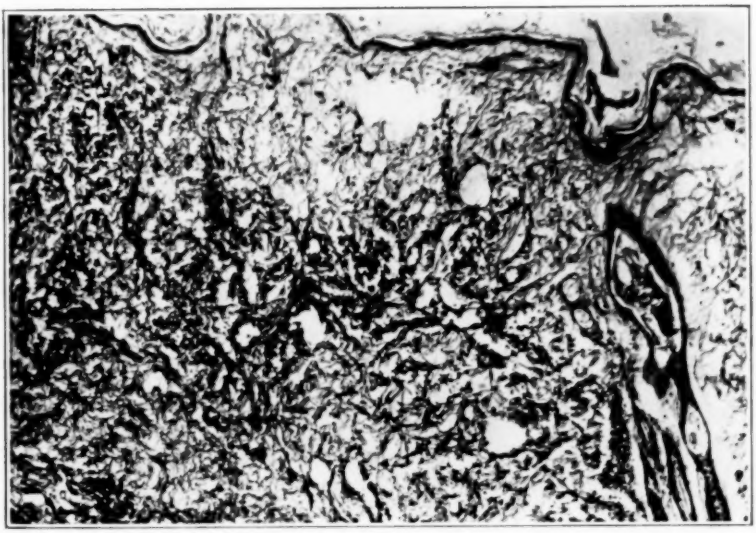


FIG. 1.—Section of skin (dog) removed 1 hour after subcutaneous injection of a saline suspension of the organisms. The section shows clumping of the bacteria, edema, but no phagocytosis.

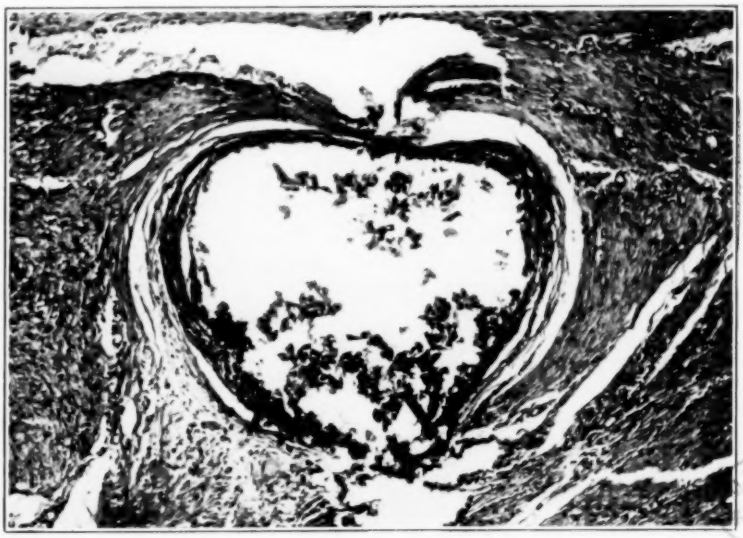


FIG. 2.—Section from an area of dog's stomach through which an infected thread had been passed 28 days before necropsy. There is no evidence of phagocytosis present. There is an absence of foreign body giant cells.

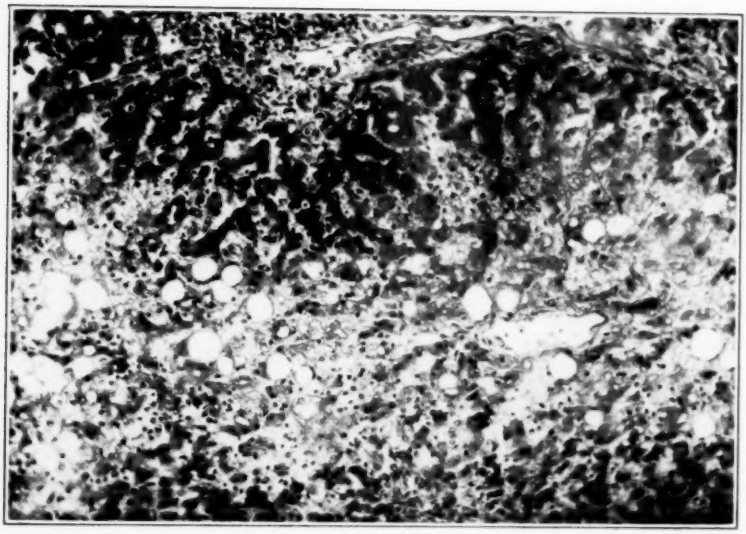


FIG. 3.—Section through dog's liver killed 22 hours following anaphylactoid reaction from which he had recovered very little. There is destruction of the central liver cells with edema and swelling of the peripheral cells of the liver lobule.

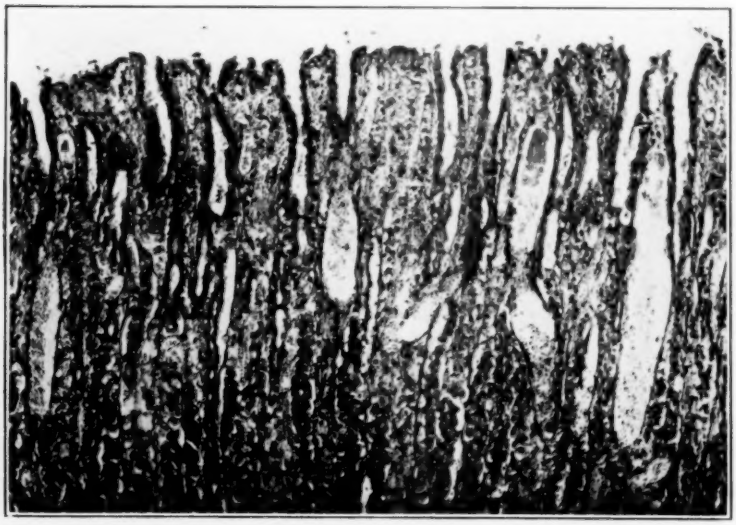


FIG. 4.—Section shows marked congestion of mucosa in cardia of stomach. Dog was killed 24 hours following an anaphylactoid reaction from which it had never fully recovered.

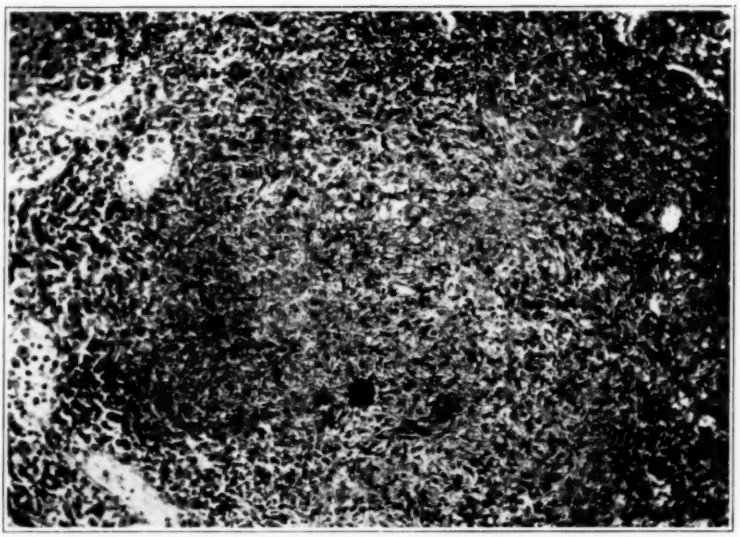


FIG. 5.—Section through lymph node of mouse which shows changes similar to that in Fig. 4, with the exception that there is more fibrosis present. It probably indicates a later stage in the same process.

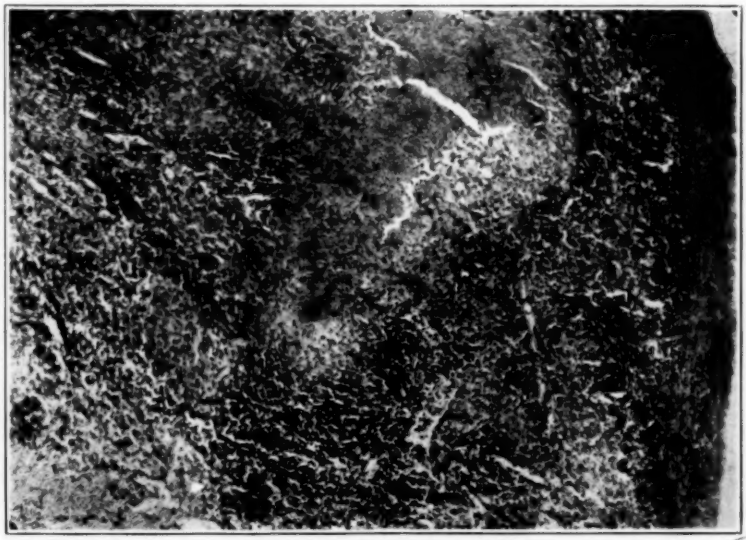


FIG. 6.—Section through spleen of rabbit showing small area of necrosis. This spleen showed a chronic splenitis throughout.

OF MICH.

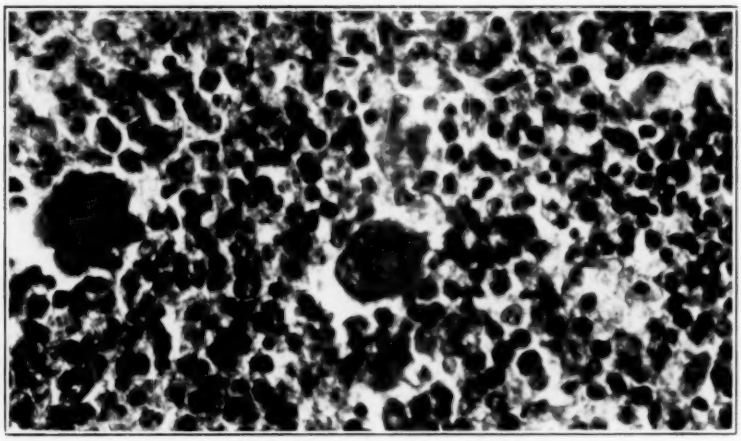


FIG. 6a.—High power of Fig. 6. Megakarocytes, not showing in low power section.

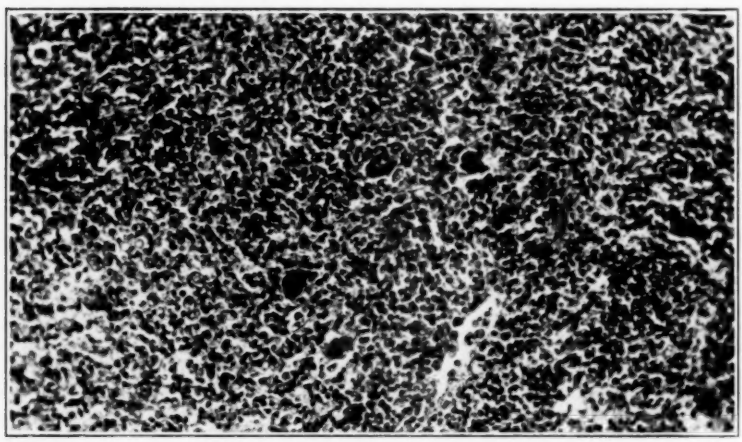


FIG. 7.—Section through spleen of mouse showing numerous megakarocytes. There is evidence of chronic splenitis present.

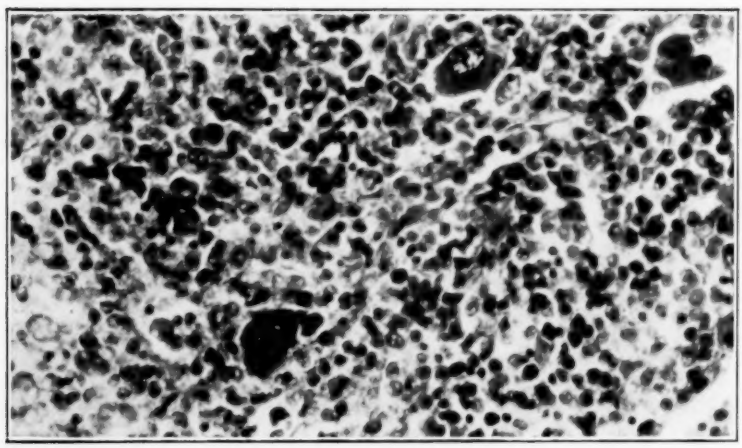


FIG. 7a.—High power of Fig. 7.

of inoculated slants, and injecting it intravenously in the dog. No reaction was obtained.

Dogs not previously inoculated with the organism were next given intravenous injections. The same type of reaction was obtained. One dog died during the night following the injection, and at autopsy the findings were about the same, although not so noticeable as those on the dogs that had previously been inoculated. Several of the uninoculated dogs were sacrificed and presented the same findings as in the previously inoculated dogs, although never so marked. Likewise the reaction of the living uninoculated dog was not so severe as in the dogs previously inoculated. An attempt was made to determine the M. L. D. of the organism, but due to animal variation, this was not very satisfactory. For instance young dogs do not react as severely and immunity can be built up in the dog by frequent small doses of the organism. In one dog the first injection was approximately nine billion organisms per cc. per kilo, which had previously killed dogs. The dog became very ill from this injection but did not die. Two days later thirteen billion organisms per cc. per kilo were given. This time the dog became ill but not so ill as on the first injection. The next day eighteen billion organisms per cc. per kilo were given. The dog became only slightly ill. Then the following day the same dog was given twenty-five billion per cc. per kilo without effect. The dogs also lose this immunity after an interval of time. In one dog a fairly large dose of organisms was given and a severe reaction developed. Three weeks later about the same number of organisms were again injected and the dog developed a reaction as severe as the first one, if not more severe. This same loss of immunity has been observed on other dogs. The length of time necessary for the loss of this immunity has not been determined. Probably one should not interpret this as an anaphylactic reaction, but rather a sensitivity of the animal either to an endo- or exotoxin, or metabolic product of the organism. It would seem that this sensitivity could be increased. On rabbits which had been injected with gradually increasing numbers of organisms, the injections being made every 10 days, an occasional animal would be killed on a repeated injection but never on the first injection. This together with the fact that the most severe reactions were obtained on the previously inoculated dogs would seem to show that the sensitivity can be increased.

Another finding of interest in some of the rabbits that had had a number of intravenous injections was the various changes found in the spleen. Sections showed a marked increase in fibrous tissue, the presence of large mononuclear cells and foreign body giant cells, a pathologic picture not unlike that of early Hodgkin's disease or tuberculous splenitis. This same type of change was also found in a number of mouse spleens. This finding, however, is not at all con-

stant, and whether it represents the specific reaction of the rabbit and mouse to this organism, or whether the same pathology is produced by other organisms, cannot definitely be determined.

In injecting rabbits intravenously with gradually increasing doses for the purpose of obtaining a high titer serum, 10 were accidentally killed by the dosage. All of them at autopsy showed a complete disintegration of the cardia of the stomach. This was probably the result of previous sensitization; and the rupture of the stomach was the only apparent cause of death.

In a number of dogs white blood cell counts were made to determine the blood reaction following intravenous injections. The typical response in 4 dogs was as follows:

	White blood cells.
Before injection	12,600
Four hours after injection	4,400
Eight hours after injection	26,400
Twenty-four hours after injection	42,000
Forty-eight hours after injection	43,000
Seventy-two hours after injection	39,000

An anaphylaxis-like reaction was present in all of these dogs. The immediate fall in leukocytes may be attributed to a negative chemotactic factor. The later increase may be due to the destruction of liver cells. Livers examined 4 hours after injection showed only edema and congestion of the liver cells. Those examined 8 hours after injection showed beginning central destruction of hepatic cells. So it seems as though the increase in leukocytes ran parallel with the increase in hepatic cellular destruction.

The toxin of high intestinal obstruction obtained by alcoholic precipitation when injected intravenously in dogs gives the same blood picture.

Discussion. The question may be brought up as to whether the organism used is pathogenic. The fact that there were no tissue changes around the infected threads demonstrates that the reaction of tissue to this organism is different from that of other organisms. Can there not be tissue damage without the usual signs of inflammation, that is, tumor, calor, rubor et dolor? If the tissue had reacted as it would normally to the non-infected thread, then there would have been a few round cells and some foreign body giant cells present directly around the thread. As these were absent, it would be logical to assume that the bacteria present in the thread or their products prevented a cellular infiltration, in other words exerted a negative chemotactic influence. There is very little to be found in the literature on negative chemotaxis, but there is no reason to doubt that it exists.

Conclusion. It has been demonstrated that there is a definite animal reaction towards the organism (streptococcus) and that this reaction can be made more severe by previously inoculating the

animal with the organism, and that an immunity can be developed in the animal by frequent injections at daily intervals. This type of sensitivity which the animal develops may well explain the periodicity of symptoms presented by ulcer patients. It would also explain the local reaction which occurs when vaccine therapy is instituted.

REFERENCES.

1. Shwartzman, G.: J. Exp. Med., 1930, **51**, 571.
2. Saunders, E. W.: Arch. Int. Med., 1930, **45**, 347.
3. Saunders, E. W.: Ann. Surg., 1930, **91**, 222.
4. Saunders, E. W.: Am. J. Cancer, 1931, **15**, 2745.
5. Saunders, E. W.: Ann. Surg., 1932, **95**, 327.

PNEUMONIA IN NEWBORN AND STILLBORN INFANTS.

By Margaret Warwick, M.D.,
PATHOLOGIST TO THE MILLARD FILLMORE HOSPITAL,
BUFFALO, N. Y.

Pneumonia in the newborn does not receive the consideration which it deserves, and may even be overlooked at the autopsy table. Johnson and Meyer,[11] in 500 consecutive autopsies upon the newborn, found pneumonia in 97 (19 per cent); Hess-Thaysen[7] found 8 per cent in one series of 49, and 42 per cent in a later group of 32, Browne[2,3] found it in 26 per cent of 80 autopsies. Cruickshank,[4] in an investigation of 800 deaths in infants dying during the first month of life, found 197 cases of pneumonia (25 per cent) and he concludes that it is the most common of the infective lesions found in the newborn infant. Hook and Katz[9] found it in 22 of 73 infant deaths (33 per cent); and Kaldor[12] in 12 of 39 autopsies (30.7 per cent).

At this hospital, in 240 consecutive autopsies upon infants, stillborn or dying during the first 2 weeks of life (excluding 18 that were badly macerated), 43 cases of pneumonia were found (18 per cent). The lungs of these cases presented a varied appearance, but in none could a diagnosis of pneumonia be made, with certainty, upon the gross examination alone. Some of the lungs were uniformly red and firm, but not solid enough for a typical consolidation. The usual picture was that of a patchy dark red color, sometimes alternating with the gray of well aërated lung tissue, the dark areas being firmer in consistency. The lesions were always bilateral, but of unequal involvement with, sometimes, only a single patch in one of the lungs, and no relationship to lobes. Usually the darker areas resembled hemorrhage, while the uniformly firm and dark red lungs resembled atelectasis with congestion. In no case was there an associated pleuritis. Of the series of 43, 31 (72 per cent) floated in water.

The microscopic appearance also showed great variation. The alveoli might be well distended or the lung might be atelectatic. The lumina of the alveoli contained polymorphonuclear leukocytes in variable numbers and, sometimes, these cells infiltrated the thickened alveolar walls. Also, there were often numerous red blood cells, desquamated endothelial cells and, frequently, the constituents of amniotic fluid which had been aspirated into the lungs. Sometimes the exudate was present in bronchi where the deeply folded lining showed that they had never been distended with air. In the majority of the cases the exudate was formed around the constituents of amniotic fluid. Also, frequently, the exudate and the foreign material from the amniotic fluid were grouped in the middle of an area of atelectasis.

As to the age of the 43 pneumonic infants in this series (Table 1) 10, almost $\frac{1}{4}$, were stillborn; 8 lived less than 12 hours and 6 less than 2 days. As pneumonia could hardly develop in less than 2 days, 24 (55.7 per cent) must have been affected while still in the uterus. Twelve more lived less than 3 days, and these, too, doubtless showed a beginning of the process before they had started their separate existence. Only 7 lived longer than 4 days. So this particular type of pneumonia in newborn infants seems to appear at birth or shortly afterward and, very rarely, is found in deaths after the 4th day.

TABLE 1.—AGES OF THE PNEUMONIC CASES.

	Number.	Per cent.
Stillborn	10	23.3
Less than 12 hours	8	18.7
From 1 to 2 days	6	14.0
2 to 3 "	12	28.0
3 to 4 "	4	9.4
4 to 5 "	1	2.2
5 to 6 "	1	2.2
9 to 10 "	1	2.2
Total	43	100.0

It is of interest to find that this condition occurred in 2 infants of only 5 months' gestation, weighing 500 and 600 gm. respectively. They had only primitive alveoli which resembled bronchi and yet in their lumina were found collections of polymorphonuclear leukocytes. Hook[8] mentions a similar case, so it is evident that an infant may be affected any time during the last half, at least, of its intrauterine life.

Lesions other than the lung condition are shown in Table 2. In 20, only the lungs showed anything of interest. In 21, the traumatic lesions of difficult birth were found. The most common was cerebral hemorrhage, present in 17 (40 per cent). In only 2 (5 per cent) were other pathologic lesions found and these were congenital defects.

TABLE 2.—PATHOLOGIC FINDINGS IN THE PNEUMONIA SERIES.

	Number.	Per cent.
Pneumonia alone	20	46.5
Cerebral hemorrhage	17	39.5
Hemorrhage in adrenals	2	4.7
Hematoperitoneum	2	4.7
Cardiac defect	1	2.3
Monstrosity	1	2.3
Total	43	100.0

With this high percentage of traumatic lesions present, it is of interest to look into the type of deliveries of these infants (Table 3). Only ¼ had spontaneous deliveries with an average length of 13

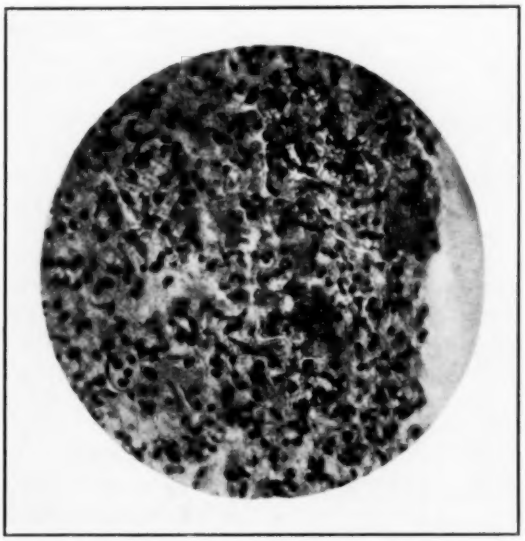


FIG. 1.—Infant lung filled with fluid, cornified epithelium and polymorphonuclear leukocytes. (× 50.)

hours, and 1 of 52 hours. Of especial interest are 3 delivered by Cesarean section. In these 3, at least, the membranes were not ruptured before birth, and the infant could not have aspirated infectious secretions during its passage down the vaginal canal.

TABLE 3.—METHODS OF DELIVERY IN THE PNEUMONIA SERIES.

	Number.	Per cent.
Version and extraction	14	32.5
Spontaneous	11	25.5
Forceps	10	23.5
Extraction of breech	3	7.0
Cesarean section	3	7.0
Extraction with forceps	2	4.5
Total	43	100.0

TABLE 4.—POSITIONS IN THE PNEUMONIA SERIES.

	Number.	Per cent.
R.O.P.	12	27.9
L.O.A.	9	20.9
Breech	8	18.6
Unknown	7	16.3
R.O.A.	4	9.3
L.O.P.	3	7.0
Total	43	100.0

The birth positions (Table 4) show a high preponderance of the unusual. The weight of the affected infants (Table 5) show a wide variation. Three weighed less than 1000 gm. and 18 (41 per cent) weighed more than 3000 gm.

TABLE 5.—BODY WEIGHTS IN THE PNEUMONIA SERIES.

	Number.	Per cent.
Less than 1000 gm.	3	7.0
1000 to 2000 "	7	16.3
2000 to 3000 "	12	27.9
3000 to 4000 "	17	39.5
4000 to 5000 "	1	2.3
Unknown	3	7.0
Total	43	100.0

A very constant finding in the lungs of these infants was the presence of the constituents of amniotic fluid. This is not unusual and attention has already been called to it by various observers. It is now an accepted fact that more or less complete respiratory movements may occur while the infant is still in the uterus. Ahlfeld[1] thinks that the fluid may be sucked down into the bronchi and again expelled. Reifferscheidt[14] believes that respiratory movements take place with the glottis closed, and that the power of suction is so slight that that the *liquor amnii* reaches, at most, only the nasal cavity or the entrance to the larynx, whence it may be sucked down into the lungs by the first breath after birth. Hook and Katz[9] think that they have found successive invasions into the lungs. In this series, constituents of amniotic fluid were found in many infants who were born dead and in 2 of these there were signs of beginning maceration, showing that the infant must have been dead for some time before it started down the birth canal. Therefore, in 2 cases at least, the amniotic fluid must have reached the lung alveoli without the infants ever having drawn a breath of the outside air.

The majority of observers feel that the presence of large amounts of amniotic fluid in the lungs indicates a fetal asphyxia where there has been a stimulation of the respiratory center resulting in attempts at breathing while still in the uterus. Johnson gives the cause of this stimulation of the respiratory center as inefficiency of the fetal circulation for any reason, such as compression or true knots in the

cord and excessive contractions of the uterine wall. Von Reuss[18] mentions the danger of premature skin stimulation in breech deliveries or podalic version causing respirations while still in the birth canal. Kaldor blames circulatory disturbances of the mother, such as asthma, heart decompensation, drugs, anesthetics and premature separation of the placenta.

The amniotic fluid is identified in the lungs by the presence of fluid, fat from the vernix caseosa, lanugo or small hairs from the skin, cornified epithelial cells which have desquamated from the skin surface into the surrounding fluid, and the bile salts from the meconium which has passed through a relaxed sphincter into the amniotic fluid. The clear fluid offers difficulty in recognition, as it may be confused with the fluid of edema. But the amniotic fluid usually coagulates in large masses which may have the form of whirls within the alveoli. The fat may be present as isolated droplets or as a thin membrane, lining the small bronchi and alveoli (described in detail by Johnson[10]). The cornified epithelial cells offer the most conclusive proof of amniotic fluid within the lungs. They are easily identified by the routine stains, as thin sheets, sometimes flat and sometimes rolled up into small sharp rods lying within the alveoli, in large or small numbers. In some areas many alveoli are packed with them. Sometimes their nuclei can be made out. Meconium is recognized by small masses of various sizes and shapes composed of brown granules. It is thought that in asphyxia, the sphincter relaxes and allows large amounts of meconium to escape into the surrounding fluid. This same asphyxia may cause premature respirations, and large amounts of the meconium will be drawn deep into the alveoli.

Farber and Sweet[5] found evidence of amniotic fluid in 88 per cent of the lungs of the 124 infants which they examined and of these, it was present in large quantities in 15 per cent. Johnson and Meyer,[11] in their series of 500 cases found evidence of amniotic fluid in 39 cases aside from the series of 97 pneumonia cases (27 per cent). In this series of 240, some one or more of the constituents of amniotic fluid were seen in 175 (73 per cent) (Table 6). Cornified epithelial cells or masses of bile salts (usually but not always occurring together), *i. e.*, absolute proof of foreign material, were found in 157 (65 per cent). Of the 240, in only 83 (34 per cent) were no epithelial cells or meconium found.

TABLE 6.—ASPIRATED AMNIOTIC FLUID IN TOTAL SERIES.

	Number.	Per cent.
Evidence of amniotic fluid	175	73
Meconium (alone or with epithelium)	141	59
Epithelium (alone or with meconium)	61	25
Fluid alone	77	32
Meconium or epithelium	157	65
No amniotic fluid (not even fluid alone)	65	27
No epithelium or meconium	83	34

In the 43 pneumonic cases, evidence of amniotic fluid was found in 38 (88 per cent), a larger number than in the total series. Of the 3 common constituents of amniotic fluid, the most frequent was bile salts, seen in 30 (70 per cent). Cornified epithelium was seen in 21 (49 per cent) and fluid in 14 (33 per cent). (See Table 7.) In only 5 cases (about 12 per cent) was there no evidence of amniotic fluid. In 1 of these cases, that of a premature infant with primitive alveoli, some brown granules, which might have been bile salts, were found within the polymorphonuclear leukocytes. At this stage of development, the bile might not have the color which, later, might attract attention. That leaves only 4 in which there appears to be no amniotic fluid, but an extensive exudate might have obscured the foreign material.

TABLE 7.—ASPIRATED AMNIOTIC FLUID IN THE 43 PNEUMONIC CASES.

	Number.	Per cent.
Aspirated amniotic fluid present	38	88
Constituents occurring alone or together:		
Meconium	30	70
Epithelium	21	49
Fluid	14	33
Aspirated amniotic fluid not present	5	12

The relationship of aspirated foreign material, such as amniotic fluid, to pneumonia occurring *in utero* or in the first few days of life, is a question over which there is much controversy. Hess-Thaysen[7] says that there is no relationship, that foreign material may give a reaction which is very different from a pneumonia which is the result of bacterial infection. Johnson and Meyer[11] feel that aspirated amniotic fluid will not cause pneumonia because, "the epidermal cells have been found in lungs for several days without any sign of inflammation. They were not attacked by phagocytes, nor do they cause formation of foreign body giant cells, but they appear to undergo a slow dissolution." But they also say, "on the other hand, choking off the air passages by a large amount of aspirated material may lead to a serious condition of asphyxia, if the child survives birth." They tried injecting amniotic fluid into the air passages of rats but were unable to produce any pneumonia. Cruickshank[4] says, "Foreign substances can predispose to pneumonia, and meconium is often seen in these lungs." Von Reuss[18] in discussing the presence of amniotic fluid in the infant's lungs says, "Later, is danger of inflammation in the atelectatic lung." Hook and Katz[9] are not prepared to give an opinion, but admit the possibility. It is a well known fact that the amount of this aspirated material varies materially. Also it is evident that the various constituents of amniotic fluid may vary in their relationship to each other and, consequently, may vary in irritating qualities. It is easy to believe that just the fluid part of the *liquor amnii* might not be irritating, while large masses of bile salts might be. Also an acid or alkaline

fluid might set up an inflammatory reaction of a chemical nature. Winternitz[17] has shown that a typical pneumonia can be produced by poison gases or the insufflation of dilute acid. Pierson[13] produced pneumonia by injection of iodized oil into the bronchi, and says that the oil may remain in the lungs and cause recurrent pneumonia, especially in young infants of poor vitality. Cornified epithelium could produce a mechanical as well as a chemical irritation, because of its hardness and being rolled up into little sharp rods. Most certainly sharp-cornered cornified epithelium and bile salts from the meconium would have a more irritating effect than iodized oil.

If aspirated amniotic fluid is not the cause of pneumonia in the newborn, other causative agents must be considered and of these, bacteria is the most frequently mentioned. The majority of observers feel that these pneumonias are caused by bacteria which enter with the liquor amnii. They discredit the placental route, as the mothers show no evidence of infection, and as no other organs of the body are affected. The frequent presence of polymorphonuclear leukocytes both in the bronchi and alveoli, points to aspiration and, consequently, they must have been in the amniotic fluid from some source. Also bacteria are frequently found in the centers of aspirated masses of amniotic fluid, but never in the bloodvessels, as they would be if the infection had been by the placental route. Hook and Katz[9] found bacteria in 9 of their 14 cases of pneumonia. Johnson and Meyer[11] in 25 antenatal cases found bacteria in only 8; but in a series dying a few days after birth, they found 18 of 29 containing bacteria. In the present series with the lung sections stained by Rosenow's modification of Gram's stain, only 11 of the 43 (25.5 per cent) showed bacteria. If bacteria were the cause of this pneumonia, they should appear in more than $\frac{1}{4}$ of the cases.

Of these 11, only 2 were stillborn, 1 lived 22 hours and the others lived 2 days or more. This is significant because in those living more than 2 days, there is always the possibility of bacteria having entered during birth or shortly afterward, and in only 3 of these can one be sure that the infection occurred *in utero*. When Table 8 is compared to Table 1 it is seen that of the 24 infants which were stillborn or lived less than 2 days, only 2 (5 per cent) showed the presence of bacteria. Of these 2, the autopsies were done 15 and 9 hours after death. Also 2 of these showed large bacilli which suggested non-pathogenic bacteria which might be secondary invaders. Also, in 1, the membranes were ruptured only 20 minutes before delivery, this excluding the possibility of infected amniotic fluid being the cause of the pneumonia. In the others the membranes ruptured 48 and 26 hours before delivery which gives too little time for the *liquor amnii* to become infected, to be aspirated into the lung and then start a pneumonia which would develop so that it would be easily demonstrable at birth or during the first days of life.

Rosenow[16] has found streptococci in the fetuses of animals which

he had injected with streptococci from influenzal epidemics and he thinks that this may have taken place through unrecognized lesions in the placental bed. He[15] feels that streptococci during influenzal epidemics have unusual powers of penetration and he suggests that in these cases of pneumonia in the newborn, the mother might have had a light influenzal attack or even have been the carrier of bacteria which, having unusual characteristics during an epidemic, might invade the body of the fetus and cause a pneumonia.

FIG. 2.—Pneumonia in lung of infant who lived 5 hours. (× 200.)

It was noted that the pneumonias in this series usually occurred in groups and during the season in which colds and influenza are the most prevalent (Table 9). The July cases were in groups and may have represented a summer epidemic. In contrast to this, the deaths of the entire series did not show any seasonal incidence.

TABLE 8.—AGE OF PNEUMONIA CASES SHOWING BACTERIA.

	Number.	Per cent.
Stillborn	2	18
Less than 1 day	1	9
2 to 3 days	6	55
3 to 4 "	1	9
4 to 5 "	1	9
Total	11	100

Johnson and Meyer[11] and also Hook and Katz[9] think that pneumonia in the newborn is caused by the aspiration of amniotic fluid which has become infected because of premature rupture of the

membranes. Hess-Thaysen[7] agrees but feels that it may also be caused by the aspiration of infected vaginal secretions during the passage down the birth canal. Johnson and Meyer[11] examined 9 of the cords and placentas of pneumonia cases in infants and found 6 with acute inflammation. Of this series, a few placentas, taken at random, were examined and in none were acute inflammatory changes found.

TABLE 9.—SEASONAL INCIDENCE OF THE PNEUMONIA CASES.

	Number.	Per cent.
January	4	9.3
February	6	14.0
March	8	18.6
April	4	9.3
May	4	9.3
June	1	2.3
July	6	14.0
August	1	2.3
September	1	2.3
October	1	2.3
November	2	4.7
December	5	11.7
Total	43	100.0

TABLE 10.—RUPTURE OF MEMBRANES IN PNEUMONIA SERIES.

	Number.	Per cent.
Unknown	11	25.6
0 to 25 minutes before birth (av., 12 minutes)	16	37.2
1 to 15 hours before birth (av., 6.6 hours)	11	25.6
A few days before birth	5	11.6
Total	43	100.0

In 62 per cent of our pneumonia cases, we can be certain that the membranes did not rupture long enough before delivery to allow the possibility of the amniotic fluid becoming infected from the outside. In only 5 (11.6 per cent) could there have been a rupture of the membranes long enough before delivery to have caused a pneumonia in the infant. Johnson and Meyer[11] bring up the possibility of infection taking place from the cervix through intact membranes, and also the possibility of one or several ruptures which were too small to be detected, but which might allow the entrance of bacteria. He also mentions the possibility of strong antiseptic solutions used to cleanse the vagina, being able to set up a chemical irritation which might be mentioned as a cause of the pneumonia. But why might not irritating amniotic fluid be as logical as antiseptic solutions? Furthermore, in 3 of our cases, delivery was before labor started, by Cæsarean section.

Perhaps the etiology of pneumonia need not be due to any one factor but rather to more than one. Perhaps infected amniotic fluid may explain one case of pneumonia, while irritating amniotic

fluid which had been aspirated might explain another. It is a well known fact that pneumonia in adults can be caused by bacteria of different strains as well as by different varieties. Also we know that it may be caused by poisonous gases or even by iodized oil. A slight overdose of silver nitrate in a baby's eye may cause a profuse exudation of polymorphonuclear leukocytes, so why could not masses of sharp, hard epithelial cells or hairs or masses of bile salts cause a similar exudate in the lungs? The aspirated amniotic fluid constituents may vary markedly in amount and in the ratio of the different constituents; perhaps the amniotic fluid may also vary markedly in toxicity or chemical reaction. Bile salts are irritating to adult tissues and they would be doubly so in the sensitive lungs of a premature or newborn baby.

Individual resistance can vary markedly, so might infants vary in susceptibility to irritating substances in the amniotic fluid. Also there must be a great variation in the amounts of fluid which may be aspirated. A baby which has had asphyxia due to some abnormal condition in the mother, and which has consequently aspirated a large amount of amniotic fluid, would probably have a lowered resistance which would make it an easy prey to irritating chemicals or to invading bacteria. Also, an infant which has passed through a long and difficult birth, possibly with some mechanical interference, must be at a disadvantage in its adjustment to its new life and thus be an easy prey to bacteria or to irritating material in the lungs.

An infant's lungs plugged by amniotic fluid constituents would be a fertile field for bacteria entering at the time of birth or shortly after, especially if the infant were subnormal or damaged at birth. A normal infant, which has passed through a quick, spontaneous birth, might have resistance enough to overcome such bacteria.

The relationship of atelectasis to pneumonia has already been pointed out. Henderson[6] believes that pneumonia in the newborn might be avoided by complete aëration of the lungs, while Cruickshank[4] and von Ruess[18] agree that atelectasis predisposes to pneumonia.

In this series, atelectasis was frequently associated with the pneumonia. Areas of atelectasis, large and small, were seen in 32 of the 43 (74 per cent). Lungs filled with amniotic fluid will expand with difficulty. In many of this series, aspirated amniotic fluid was frequently found in the center of the atelectatic areas, while many such areas showed also an exudation of polymorphonuclear leukocytes. At the present time, the main etiologic factor seems to lie between bacteria and irritating amniotic fluid. There are certain facts in favor of bacteria as a primary cause, but the difficult thing is to find a logical explanation of their entrance into the lungs of the unborn infant. This may be either by entrance through the placenta

from a mother who has had a light case of influenza, or who is a carrier of those germs, or by infected amniotic fluid. The facts favoring bacteria as the cause of pneumonia in the newborn infant are given below:

1. Bacteria are usually the cause of exudation of polymorphonuclear leukocytes and of pneumonia.
2. Bacteria can be demonstrated in some of the pneumonic lungs.
3. In some, possible sources of infection are found, such as premature rupture of the membranes or light respiratory infections in the mother.
4. Some of the cases of pneumonia occur in groups during the months in which respiratory infections are the most prevalent.
5. Amniotic fluid is very frequently found in lungs where there is no evidence of pneumonia.

On the other hand, equally good reasons may be found for the possibility of uninfected amniotic fluid being the etiologic factor and these are also given below:

1. Chemicals may cause an exudative inflammation and also pneumonia.
2. A large percentage of cases show no demonstrable bacteria.
3. Masses of aspirated amniotic fluid are often found surrounded by numerous polymorphonuclear leukocytes in the midst of an atelectatic lung.
4. The pneumonia is often associated with atelectasis.
5. Amniotic fluid may vary markedly in constituents and in irritability.
6. Infants with other physical handicaps are often affected.
7. In some cases no convincing possibility of entrance of bacteria is seen.

Conclusions. Pneumonia in newborn infants is a definite entity and should be recognized by obstetricians, pediatricians and pathologists. It usually begins *in utero* or during birth. The majority of the victims have physical handicaps and so the pneumonia may be the result of lowered resistance. The exciting cause is as yet uncertain, but seems to rest between bacteria contaminating the amniotic fluid or an irritating amniotic fluid, particularly when it contains large amounts of bile and cornified epithelial cells. Present evidence seems to favor the latter.

REFERENCES.

1. Ahlfeld, quoted by von Reuss, A. R.: Diseases of the Newborn, New York, William Wood & Co., 1929.
2. Browne, F. J.: Brit. Med. J., 1922, **1**, 469.
3. Browne, F. J.: Ibid., 1922, **2**, 590.
4. Cruickshank, J. N.: Child Life Investigations, London, His Majesty's Stationery Office, 1930.
5. Farber, S., and Sweet, L. K.: Am. J. Dis. Child., 1931, **42**, 1372.
6. Henderson, Y.: J. Am. Med. Assn., 1931, **96**, 495.

7. Hess-Thaysen, T. E.: Jahrb. f. Kinderh., 1914, **79**, 140.
8. Hook, H.: Beitr. z. path. Anat. u. z. allg. Path., 1927, **77**, 456.
9. Hook, H., and Katz, K.: Virchow's Arch. f. path. Anat., 1928, **267**, 571.
10. Johnson, W. C.: Proc. New York Path. Soc., 1923, **23**, 138.
11. Johnson, W. C., and Meyer, J. R.: Am. J. Obstet. and Gynec., 1925, **9**, 151.
12. Kaldor, J.: Am. J. Obstet. and Hyg., 1933, **25**, 113.
13. Pierson, J. W.: J. Am. Med. Assn., 1932, **99**, 1163.
14. Reifferscheidt, K.: Deutsch. med. Wchnschr., 1911, **19**, 877.
15. Rosenow, E. C.: J. Dent. Res., 1919, **1**, 230.
16. Rosenow, E. C.: J. Inf. Dis., 1920, **26**, 469.
17. Winternitz, M. C., Smith, G. H., and McNamara, F. P.: J. Exp. Med., 1920, **32**, 199.
18. Von Reuss, A. R.: Diseases of the Newborn, New York, William Wood & Co., 1929.

OBSERVATIONS ON THE PRODUCTION OF PAIN AND FATIGUE IN MUSCULAR ISCHEMIA AND THEIR RELATIONSHIP IN ANGINA PECTORIS.

By Louis B. Laplace, M.D.,
FELLOW IN MEDICINE, THE NATIONAL RESEARCH COUNCIL,
AND
Martin P. Crane, M.D.,
INSTRUCTOR IN MEDICINE, UNIVERSITY OF PENNSYLVANIA MEDICAL SCHOOL AND DENTAL SCHOOL; ASSISTANT VISITING PHYSICIAN, MISERICORDIA HOSPITAL, PHILADELPHIA.

(From the Medizinische Universitätsklinik, Leipzig, Germany; Director, Professor P. Morawitz.)

The nature of the pain produced by muscular ischemia in the human limb as studied by MacWilliam and Webster,[1] Lewis, Pickering and Rothschild[2] and Kissen[3] has been considered by Lewis[4] in the interpretation of angina pectoris which is now generally believed to be associated with myocardial ischemia. Obstruction of the coronary circulation, however, does not always produce pain[5] and the reasons for this have not yet been adequately demonstrated, although anastomoses with the Thebesian[6] or pericardial vessels[7] and low constitutional sensitivity to pain[8] have been proposed as possible explanations. The pain produced by ischemia of skeletal muscle may also vary in its intensity and under certain circumstances may not occur at all. Kissen has called attention to the fact that the pain is more severe when the oxygen content of the arterial blood is low.[3] In the following observations it will be shown that fatigue is also a factor which largely determines the severity of the pain developing in ischemic muscle. These results help to explain the inconstancy with which angina pectoris occurs in the presence of coronary arterial disease.

Methods. The investigation consisted essentially in a study of the pain arising in the human limb during repeated muscular contractions in the

presence of varying degrees of ischemia. The exercise chosen was that of a simple gripping movement exerted upon a hand ergometer once per second. Compression of the grip of the ergometer lifted a weight over a distance of 12 mm. and was recorded upon a small kymograph. The standard experiment undertaken by all subjects for purposes of general comparison was performed by the right arm lifting a 10 kg. weight. The circulation was occluded by a Riva Rocci armlet which was rapidly inflated to a pressure above the systolic and exercise commenced immediately. Modifications of this procedure, as indicated in the text, consisted of exercise performed with the circulation free and with the arm rendered ischemic by the application of an elastic bandage. Variations in the weight lifted and comparison of results obtained upon the right and left arms were also made. Rest periods of at least a half hour were allowed between experiments upon the same arm.

In order to evaluate the influence of constitutional sensitivity upon the pain of muscular ischemia, observations were made upon a series of 36 subjects, 6 women and 30 men, of widely varied physical and psychic types. Of these, 16 were healthy while 20 were patients from the medical service of St. Jakob's Krankenhaus (Leipzig). The latter group was selected to include subjects who complained of severe pain, in some cases of organic origin, in others without demonstrable pathologic background; also patients in whom organic disease was not manifested by pain. Of particular interest are 7 subjects who had angina pectoris and 5 others who complained of cardiac palpitation and sensations of precordial pressure.

Results. It has been shown[1,2] that simple arrest of the circulation to the human limb may produce sensations of numbness and tingling but that pain comparable to that occurring with muscular effort does not develop. If continuous muscular effort follows however, such as lifting a 10 kg. weight on the ergograph, characteristic pain soon appears and may increase to an extreme degree of intensity.

Onset of Pain. The moment of onset of acute pain was not always easy to indicate as it was usually preceded by a vague sense of discomfort which gradually increased in intensity. The times of onset of these first manifestations, as nearly as they could be ascertained, are indicated in Table 1. No relationship is apparent between the onset of pain and the duration of exercise, rapidity of development of pain or its ultimate intensity. In subject H. E. for example, pain appeared 125 seconds before developing to a degree of intolerable intensity, while in subject F. R. the onset of pain was so severe as to preclude further exercise.

Development of Pain and Fatigue. If exercise was continued (lifting the 10 kg. weight with the circulation arrested), a point was ultimately reached at which the subject could not or would not proceed further. In some cases the pain was so severe that exercise was stopped because further contractions were agonizing although muscular weakness had not yet attained a degree sufficient to prevent a considerably longer period of exercise. In other instances fatigue was the outstanding factor and the subject became physically unable to lift the weight again although pain was not always severe.

Sometimes it was impossible for a subject to state with certainty whether he stopped because of pain or fatigue. Two further criteria sufficed to determine this point.

TABLE 1.—STANDARD EXPERIMENT ON 36 SUBJECTS.

(Right arm. Circulation occluded. Weight, 10 kg. Contractions, 1 per sec.)

Subject.	Sex.	Onset of pain, sec.	Duration of work, sec.	Stopped by.	Character of pain.	Diagnosis.
H. O.	M	47	104	Fatigue	Endurable	Normal.
S. A.	M	56	128	Fatigue	Endurable	Normal.
K. U.	M	60	88	Fatigue	Endurable	Normal.
T. H.	M	90	147	Fatigue	Endurable	Normal.
C. R.	M	62	120	Fatigue	Cumulative	Normal.
L. A.	M	31	132	Fatigue	Cumulative	Normal.
L. E.	M	83	151	Fatigue	Cumulative	Normal.
H. E.	M	36	171	Fatigue	Cumulative	Normal.
L. H.	M	36	96	Fatigue	Cumulative	Normal.
B. E.	M	30	77	Pain	Intolerable	Normal.
K. L.	M	47	120	Pain	Intolerable	Normal.
S. E.	M	80	144	Pain	Intolerable	Normal.
N. F.	F	30	62	Fatigue	Endurable	Normal.
K. A.	F	44	78	Fatigue	Endurable	Normal.
L. U.	F	36	73	Fatigue	Endurable	Normal.
J. O.	F	None	23	Fatigue	None	Normal.
K. R.	M	36	48	Fatigue	Endurable	Angina pectoris.
S. I.	M	27	67	Fatigue	Endurable	Angina pectoris.
B. I.	M	48	69	Fatigue	Cumulative	Angina pectoris.
M. E.	M	44	57	Pain	Intolerable	Angina pectoris.
F. R.	M	43	43	Pain	Intolerable	Angina pectoris.
T. R.	M	42	53	Pain	Intolerable	Angina pectoris.
M. U.	M	40	97	Pain	Intolerable	Angina pectoris.
D. R.	M	55	78	Pain	Intolerable	R.H.D. aor. reg.
W. O.	M	86	102	Pain	Intolerable	R.H.D. aor. reg.
A. M.	M	72	89	Fatigue	Cumulative	Luetic aortitis.
T. P.	M	27	120	Fatigue	Cumulative	Nervous heart.
P. O.	F	None	37	Fatigue	None	Nervous heart.
S. C.	M	48	74	Fatigue	Endurable	Bronchitis.
K. E.	F	None	58	Fatigue	None	Neurosis.
K. R.	M	20	27	Fatigue	Endurable	Anemia.
R. O.	M	25	113	Fatigue	Cumulative	Ureteral stone.
S. T.	M	53	98	Fatigue	Endurable	Peptic ulcer.
G. B.	M	94	114	Fatigue	Cumulative	Peptic ulcer.
B. R.	M	60	80	Pain ?	Cumulative	Peptic ulcer.
Z. S.	M	48	92	Pain	Intolerable	Peptic ulcer.

1. Certain characteristic differences were shown in the ergogram. When the exercise was terminated by pain, the subject was usually able to produce maximum contractions until the end of the experiment. The majority of subjects who stopped because of fatigue, however, exhibited ergograms in which the development of muscular weakness was indicated by terminal diminution in the height to which the weight was lifted, so that the curves of muscular contraction became progressively smaller.

2. As previously stated,[1,2] removal of the constricting armlet brings prompt relief, but if the circulation remains occluded pain persists for a short period in unaltered intensity. In all subjects the armlet was therefore left in place after termination of the exercise. If the subject then

insisted that pain was still intolerable, exercise was considered to have been stopped because of pain. When, however, the armlet could be endured without complaint, exercise was considered to have been stopped because of fatigue. In some cases, pain which was at first endurable suddenly increased to excruciating severity during a period of 15 to 45 seconds from the end of exercise. Although these subjects obviously stopped because of fatigue, the point of intolerable pain was not far removed. This type of pain is noted in the protocols as being "cumulative."

Experiments of the type employed here are admittedly not suitable to the study of the pure fatigue curve of human muscle, since fatigue begins long before it is exhibited upon an ergogram of limited isotonic contractions. Increasing amounts of effort are furthermore exerted by the subject to compensate for increasing muscular weakness. Accurate differentiation between degrees of fatigue was, however, unnecessary for the purposes of this study, since it was only essential to determine the point at which a subject became incapable of contracting his muscles against a particular resistance and to learn whether pain or muscular weakness was the predominant factor. Such a point is much more comparable to the beginning of cardiac insufficiency for the heart during life must also contract against a definite arterial resistance and complete cardiac fatigue occurs only at the time of death.

The results obtained on all subjects from the standard procedure of manipulating the ergograph with a 10 kg. weight in the presence of an arrested circulation are shown in Table 1, indicating a wide variation between different individuals in the intensity of the pain so produced. Thus of the 15 normal subjects, 3 stopped voluntarily because pain was said to be unbearable, while in 4 pain was of the cumulative type and close to the intolerable point, and 8 stopped because of fatigue. These appeared to have exerted themselves to the limit of their physical capability but the resultant pain was by no means unbearable.

An important factor in determining the degree to which pain may develop in the ischemic limb is therefore the concomitant development of fatigue. A relatively rapid onset of fatigue (*i. e.*, inability of the muscle to contract against a given resistance) may terminate exercise before pain becomes severe. In 4 cases fatigue was so marked that pain did not occur at all. If fatigue develops relatively more slowly however, exercise may be permitted to proceed to a point at which pain becomes agonizing. How different may be the amount of work necessary to produce either pain or fatigue in different individuals is indicated by the fact that subject F. R. developed intolerable pain in 43 seconds while subject S. E. attained this point only after 144 seconds and subject T. H. was checked by fatigue, and not pain, at 147 seconds.

To some extent the amount of work which a subject may perform in the presence of increasing pain is modified by a factor which may be called endurance. Endurance does not affect the production or appreciation of pain, but rather determines the degree of pain which the subject considers intolerable. Intolerable pain is only a relative term and varies to some extent among individuals. This variability, however, does not destroy the

value of the accompanying observations, since pain at the point of unendurability was always extremely severe while it was not severe in many cases in which the subject ceased exercise because of fatigue.

Effect of Variation in Work. Differences in the relationship of pain and fatigue may be produced in the same individual by changing the experimental conditions. The effect of altering the resistance to muscular contraction was investigated by diminishing the amount of weight lifted on the ergograph. Lightening the load to 2 kg. produced intolerable pain in all cases, apparently by increasing the number of contractions which the subject was able to perform. Results obtained in two experiments are illustrative. Exercise consisting in lifting a 10 kg. weight was terminated by fatigue in subject C. R. after 120 seconds and in subject L. A. after 132 seconds. Substituting a 2 kg. weight, these subjects were able to continue to 234 and 209 seconds respectively, but in both cases intolerable pain was produced. It is therefore clear that although diminishing the resistance to muscular contraction delays the development of pain and fatigue, it causes pain to appear relatively sooner than fatigue.

Effect of Ischemia. That the degree of ischemia also influences the relationship of pain and fatigue was shown in the following manner: In a group of normal subjects, estimations were made of the effect of exercise with the circulation free. The circulation was then arrested by inflation of an armlet and the experiment repeated. In the latter procedure a large volume of residual blood was retained in the arm which may have influenced the results. A further modification was therefore carried out: In a third experiment the arm was rendered ischemic prior to exercise by the application of an elastic bandage which was removed after inflation of the armlet. The experiments were performed upon the right arm and consisted in lifting the 10 kg. weight at the rate of one contraction per second. Characteristic results are indicated by the following protocols:

In the first experiment in which the circulation was free, subject C. R. was stopped at 145 seconds and subject L. A. at 209 seconds by fatigue. Both subjects experienced various degrees of aching sensations in the forearm but in neither case did characteristic pain appear. On repeating the experiment with the circulation arrested in the usual manner, exercise was terminated sooner by fatigue after 120 and 132 seconds respectively. The pain was severe, however, and increased to an unbearable degree shortly after cessation of work. When the arm was made ischemic in the third experiment the duration of exercise was further diminished to 101 and 116 seconds and pain of the most excruciating intensity was produced.

It appears therefore that fatigue and pain are not modified to the same extent by increasing degrees of muscular ischemia. In the presence of a free circulation fatigue is predominant and pain occurs only to a slight degree. When a condition of simple circulatory arrest obtains, both pain and fatigue are increased but pain is much

more marked. Finally, in the presence of relatively complete ischemia, increase in the manifestation of pain is so pronounced that it completely overshadows the effect of fatigue.

Effect of Differences Between Individual Muscles. Comparisons of the results obtained by carrying out the routine experiment upon the right and left arms of the same subject show that exercise may be terminated either in both arms by pain or in both by fatigue although the duration of exercise need not be the same on the two sides. In many subjects however, pain terminated exercise on one side and fatigue on the other. In such cases pain may have been associated with either the longer or the shorter period of work. A few protocols contrasting these observations are given in Table 2. In the presence of a specific degree of ischemia and constant type of work, the relative production of pain and fatigue may therefore differ not only in the same muscles of different individuals but likewise in different muscles of the same individual.

TABLE 2.—COMPARISON OF RESULTS OF STANDARD EXPERIMENT ON RIGHT AND LEFT ARM.

(Circulation occluded. Weight, 10 kg. Contractions, 1 per sec.)

Subject.	Arm.	Onset of pain, sec.	Duration of work, sec.	Stopped by.	Character of pain.
D. R.	R.	55	78	Pain	Intolerable.
	L.	48	59	Pain	Intolerable.
S. A.	R.	56	128	Fatigue	Endurable.
	L.	46	55	Fatigue	Endurable.
T. R.	R.	42	53	Pain	Intolerable.
	L.	43	53	Pain	Intolerable.
W. O.	R.	64	79	Fatigue	Cumulative.
(Left-handed)	L.	86	102	Pain	Intolerable.
L. A.	R.	31	132	Fatigue	Cumulative.
	L.	27	82	Pain	Intolerable.

Nervous Sensitivity. The possibility that the intensity of pain produced by muscular ischemia is modified by differences in constitutional sensitivity or central appreciation of pain among different individuals was investigated by comparison of the routine experiment upon a large group of subjects representing a variety of psychic types. Many were phlegmatic, others obviously neurotic, so far as these qualities could be clinically appraised. Twelve patients, including cases of peptic ulcer, ureteral calculus and angina pectoris, had severe pain as an outstanding symptom of their clinical conditions. Five others had lesser degrees of cardiac symptoms, including palpitation and sensations of precordial pressure. Both sexes were represented as well as all decades between the third and eighth. It was found that subjects exhibiting neurotic tendencies (*i. e.*, emotional manifestations, hypochondriasis, vasomotor instability and severe pain) did not show marked disposition to the development of muscular pain under the experimental conditions. For the most part, in fact, they were of the group in which exercise was stopped

by fatigue. No female subject developed intolerable pain and the majority of elderly subjects were also stopped by fatigue. The inference is not drawn from these data that the appreciation of pain is less among women or in old age than among other subjects. The probable explanation is that relative muscular weakness prevented their exercising to the point of developing severe pain. Of the 7 patients with angina pectoris, 4 developed intolerable pain. No significantly greater disposition to pain was therefore manifested by this group than was found among other subjects. Certainly the rôle of nervous sensitivity must have been negligible among the 3 subjects with angina who did not develop intolerable pain. From these observations upon the entire series it was clear that nervous sensitivity, as clinically manifested by the symptoms indicated above, does not appear to affect the pain of muscular ischemia.

Discussion. The evidence presented in the present investigation indicates that the development of both pain and fatigue in rhythmically contracting skeletal muscle is favored by arrest of the circulation, that the effect of increasing degrees of ischemia is more marked in eliciting pain than in calling forth fatigue and that the relative rate of development of pain and fatigue under constant conditions is not the same in different muscles, even of the same individual. The intensity of the pain furthermore does not appear to be affected by constitutional differences in nervous sensitivity among different subjects. Factors upon which pain of this type depends are therefore not entirely the same as those responsible for fatigue. It appears possible that pain and fatigue are independent phenomena occurring under similar conditions. Admitting, however, that they may be associated with the accumulation of the same metabolic products, fatigue may depend upon the reaction of such substances within the muscle cell and pain upon their reaction in the intercellular spaces surrounding it. The concentration of any substance is likely to be different in the two places and the threshold value of effective concentration to be different for the two phenomena. Differences between the development of pain and fatigue would therefore be modified by such changes as would affect the threshold of fatigue within the cell, the permeability of the cell wall, the threshold of sensitivity of the sensory nerve endings in the intercellular spaces or the rate of removal, mechanical or by oxidation, of metabolic products by the blood stream. Support is lent to such an interpretation by the observation that pain is quickly dissipated by restoring the circulation while a certain degree of residual fatigue persists and that although both pain and fatigue are increased by anoxemia, the former appears to be more affected by the volume of blood, static or in motion, which is presented to the tissues, than is fatigue.

Applicability to Cardiac Pain. On the basis of the foregoing observations certain inferences in regard to pain of cardiac origin

may be drawn. Angina pectoris occurs in the presence of sclerosis or other obstruction of the coronary vessels when increased work of the heart in response to increased demands upon the circulation exceeds the capacity of the coronary vessels to supply an adequate amount of blood. On this assumption there is for the individual subject a threshold rate of expenditure of cardiac energy above which pain is produced by a relative myocardial ischemia and below which it does not occur. What is obscure is, not why pain occurs, but why in many cases of advanced coronary disease it does not occur. An answer may be found in the relationship of pain to fatigue in the ischemic skeletal muscle.

In those observations in which the circulation was completely arrested the development of fatigue was able in many cases to prevent the muscles from contracting against a constant resistance to a degree sufficient to produce severe pain. In the case of the similarly contracting myocardium, to which in the majority of instances the coronary blood flow is not completely arrested but only limited, it appears possible that the development of myocardial fatigue may so restrict the energy expenditure of the heart that pain may not occur at all. The occurrence of angina pectoris may therefore depend upon the influence of the same factors which favor the production of a greater degree of pain in proportion to fatigue in the ischemic muscle. Subjects with coronary disease who develop pain on effort may be compared to the subjects who developed severe pain in the ischemic limb. Cases of coronary disease without pain may be explained by the fact that the development of myocardial fatigue prevents an increase in the work of the heart sufficient to produce pain. Exertion in such subjects causes breathlessness due to the inability of the heart to meet the demands of the circulation; but pain does not occur, because the energy expenditure of the heart is not sufficient to produce it. Attacks of angina pectoris are seldom associated with severe breathlessness because the heart is usually still maintaining an adequate circulation. Infarcted areas of the myocardium which have ceased to function might therefore cause no pain and, in the same manner, older infarcted areas, capable of limited function but which have become infiltrated with fibrous tissue, may not be able to expend energy sufficient to produce angina. The absence or disappearance of pain in many cases of coronary occlusion may be explained in this way. The rarity of angina pectoris in congestive heart failure and its observed disappearance with the onset of congestive failure may be ascribed to a reduction in the maximal work of the heart to a level insufficient to maintain an adequate circulation but below the threshold of pain production. Finally, in view of the fact that nervous sensitivity was found to be without apparent influence upon the pain of ischemic skeletal muscle, it is improbable that it is a significant factor in the production of angina pectoris.

Summary and Conclusions. 1. Observations were made in a series of 36 subjects on the relationship of ischemia to the development of pain and fatigue in the contracting muscles of the arm.

2. The development of both pain and fatigue was favored by arrest of the circulation, but the two phenomena were not affected to the same extent by different degrees of ischemia or by variations in the type of work. In many cases the relatively early development of fatigue was able to terminate exercise before the manifestation of severe pain.

3. Constitutional nervous sensitivity did not appear to affect the pain of muscular ischemia.

4. On the basis of these observations, it is concluded that constitutional nervous sensitivity is unlikely to be a significant factor in the occurrence of angina pectoris. The rarity of cardiac pain in congestive heart failure and its absence in many cases of coronary obstruction may be explained by the fact that the development of cardiac fatigue maintains the maximal work of the heart at a level below the threshold of pain production.

NOTE.—The authors wish to express their indebtedness to Prof. Max Hochrein for his assistance and criticism in the preparation of this work.

REFERENCES.

1. MacWilliam, J. A., and Webster, W. J.: Brit. Med. J., 1923, **1**, 51.
2. Lewis, T., Pickering, G. W., and Rothschild, P.: Heart, 1931, **15**, 359.
3. Kissen, M.: Proc. Soc. Exp. Biol. and Med., 1932, **30**, 114.
4. Lewis, T.: Arch. Int. Med., 1932, **49**, 713.
5. Hochrein, M., and Seggel, K. A.: Zeits. f. klin. Med., 1933, **125**, 161.
6. Bellet, S., Gouley, B. A., and MacMillan, T. M.: Arch. Int. Med., 1933, **51**, 112.
7. Hudson, C. L., Moritz, A. R., and Wearn, J. T.: J. Exp. Med., 1932, **56**, 919.
8. White, P. D.: Heart Disease, New York, The Macmillan Company, 1931.

REVIEWS.

INFECTIONS OF THE HAND. By ALLEN B. KANAVEL, M.D., Sc.D., Professor of Surgery, Northwestern University Medical School, Chicago; Attending Surgeon, Wesley Memorial and Passavant Memorial Hospitals, Chicago. Pp. 552; 216 illustrations. Sixth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1933. Price, $6.00.

SIX editions on such a specialized subject are in themselves good evidence of the value of this deservedly popular book. In addition to a simplification of the experimental and pathologic proofs offered (permitted by the increasing acceptance of concepts that were at first controversial), considerable new subject matter has been added on: "the peculiar course of infections from bites and injuries from the teeth (Koch, Mason), the pathology and treatment of metacarpophalangeal joint infections, of gangrenous infections, of injuries from indelible pencils, of cattle-hair and other peculiar infections. Chapters have been added upon the function of the hand, the use of splints, and the prophylactic treatment of injuries." E. K.

BACTERIAL INFECTION. By J. L. T. APPLETON, JR., B.S., D.D.S., Professor of Microbiology and Bacteriopathology, The Thomas W. Evans Museum and Dental Institute School of Dentistry, University of Pennsylvania. Pp. 654; 122 illustrations, 4 colored plates. Philadelphia: Lea & Febiger, 1933. Price, $7.00.

THIS book accomplishes its limited purpose. It was written to give an account of bacterial infection for those planning to engage in dental practice. The style is clear and readable. The specialized information which it contains is of considerable interest. A good index has been compiled and many references in its field have been collected. Indeed, so many are cited that one is inclined to wish that more concerned with modern general and theoretical developments in bacteriology had been included for the occasional inquiring student. D. S.

METABOLIC DISEASES AND THEIR TREATMENT. By DR. ERICH GRAFE, Professor of Medicine and Director of the Clinic of Medicine and Neurology, University of Würzburg, Germany. Translated by MARGARET GALT BOISE, under the supervision of EUGENE F. DU BOIS, M.D., Medical Director, Russell Sage Institute; Professor of Medicine, Cornell University; and HENRY B. RICHARDSON, M.D., Associate Professor of Medicine, Cornell University, New York. Pp. 551; 37 illustrations. Philadelphia: Lea & Febiger, 1933. Price, $6.50.

THE author, a well-known authority upon diseases of metabolism, has succeeded in his aim of bridging the gap between the experimental laboratory of nutrition and practice in the clinic. This edition in English is more than a translation, in that many items have been revised and brought up to date.

With the guiding principle that the end-purpose of the clinician is to furnish adequate therapy, therapeutic measures are discussed in detail. As therapy should be based upon scientific knowledge, this, too, is given where possible.

Diabetes mellitus receives the most space, and there are fine sections on obesity (and related rarer conditions such as "circumscribed" habitual overnutrition), habitual undernutrition, diabetes insipidus, gout, alcaptonuria, etc.

In any text it is well-nigh impossible to keep pace with the present rate of scientific development in certain fields. Hence, one can only forgive the author's doubt as to whether vitamin C is so simple a substance as a hexuronic acid derivative (Szent-Györgyi), and his discussion of the findings of Rygh with reference to narcotin. It has already been established that vitamin C is the former and not the latter. Unlike many German texts, the bibliography has an adequate representation of foreign authors. Du Bois' connection with this work should at once establish it as an authoritative account. It is a valuable summary of the pathogenesis, physiology and therapy of the metabolic diseases and deserves the attention of all interested in this field. D. D.

NUTRITION. By GRAHAM LUSK, Sc.D., M.D., LL.D., late Professor of Physiology, Cornell University Medical School, N. Y., former Member of the Royal Society. Pp. 142; 13 illustrations. New York: Paul B. Hoeber, Inc., 1933. Price, $1.50.

THIS posthumous volume of pocket size represents the tenth of a series of primers on medical history, published under the title of "Clio Medica." From the standpoint of leadership in his chosen field and influence as a teacher, no man was more suited than the author to the task of writing a historical account of certain phases of the ever widening science of nutrition. His former students particularly will be delighted by this essay, which recaptures and recreates the spirit of the man, for Graham Lusk had a lifelong interest in his scientific ancestors. His lectures were colorfully anecdotal.

The account embraces mainly the history of energy metabolism. From the primitive concept of four elements—fire, air, earth and water—we are transported gradually to that lofty summit where the indirect determination of the heat production by the measurement of the respiratory exchange is found to agree within 0.2 per cent with the heat output as determined by direct calorimetry. This represents perhaps the most rigidly quantitative of biologic experiments, and is a most beautiful application of the law of conservation of energy to the process of life.

No space is devoted to present-day trends in nutrition. The book is essentially a retrospect peopled by almost legendary heroes—da Vinci, Sanctorius, Lavoisier, Gay-Lussac, Liebig, Voit and Rubner. About these Olympian characters the writing is full of homage and inspirational. Once again we "see" the delightful picture of young Liebig and his teacher, Gay-Lussac, dancing around a table in sheer, joyous abandon because of a new discovery; or modest Ludwig, whose pupils were permitted to publish his discoveries under their own names. At the same time, the author's rare fairness of mind does not condone natural human weaknesses in his heroes. Thus, when he was over sixty, Berzelius berated Liebig for the latter's "poetical tendencies" and charged him with having had his head turned by the adulation of the British. This sharp criticism actually followed upon the heels of the publication of Liebig's *Thierchemie*, dedicated to the older scientist. History repeated itself. A generation later, sixty-seven-year-old Liebig wrote an article in which he criticized his pupil, Voit. The

latter's reply was so strong that "Liebig, who all his life had most vigorously assailed all opponents, broke down and cried." The author remarks that "theories are often held tenaciously and are overvalued by their proponents."

All who are interested in "that scientific medicine which affrights the spirits of those devoted to a passing empiricism" will find this short work an excellent addition to the cultural side of their medical equipment. Professor Lusk's joy in his task—his last—is transmitted in every page of the book. D. D.

THE DOCTRINE OF THE HEALING POWER OF NATURE THROUGHOUT THE COURSE OF TIME. By MAX NEUBURGER, M.D., PH.D., Vienna. Translated by LINN J. BOYD, M.D., F.A.C.P. Pp. 184, n.p., n.d. New York, 1933.

THE healing power of Nature (*vis medicatrix naturae*) is "perhaps the greatest of all problems which have occupied the physician for thousands of years." Its influence, still far from being correctly evaluated, must concern physicians today as much as those of Athens or Rome. When, therefore, one of the world's leading medical historians traces the significant facts in its history from the original sources scattered over 27 centuries and often in hidden places, and for the first time brings together the development of these views in a connected way, an event of prime importance in medical literature can be signalized. From the time when spontaneous healing and the organism's tendency to help itself was established in the Hippocratic writings, the idea has persisted with varying fortunes and modifications. Even Asclepiades, who regarded the Hippocratic method of relying on Nature as a "mediator on death," trusted to fever as a healing agent; whereas in our own times but a few years ago fever was frequently regarded as a bad symptom to be removed if possible. Rhuphos, indeed, is reported by Oribasius as wishing that he could produce fever artificially! For obvious reasons the book is chiefly concerned with theories of diseases and especially with the nature of inflammation and infection. However, such advances as Mayow's and Corrigan's recognition of cardiac hypertrophy as a response to increased work brought about by damaged valves also find their place. Naturally, perhaps, neoplasms are not mentioned. The index, containing between 300 and 400 proper names, bears mute witness to the constancy with which medicine has considered this problem of the healing power of Nature. E. K.

MODERN ASPECTS OF GASTROENTEROLOGY. By M. A. ARAFA, M.R.C.P. (LOND.), Medical Assistant to Guy's Hospital, London; Medical Tutor to the Egyptian University and formerly Senior Medical Registrar to Kasr-el-Ainy Hospital, Cairo. With a Foreword by ARTHUR F. HURST, M.D., F.R.C.P., Senior Physician, Guy's Hospital, London. Pp. 374; 79 illustrations. Baltimore: William Wood & Co., 1933. Price, $8.25.

THIS is an interesting book—essentially practical and dealing chiefly with approved methods of investigating gastro-intestinal disease. The importance in diagnosis of symptoms and physical findings is not neglected. A few diseases, such as chronic gastritis and peptic ulcer, also the ulcerative lesions of the colon, are presented rather completely, but carcinoma of the stomach is referred to only incidentally. In a chapter on cholecystography and duodenal intubation these procedures are described simply but adequately, and no unreasonable claims are made. The author properly emphasizes the fact that gall bladder disease, chronic gastritis and peptic

ulcer are the most frequent organic causes of dyspepsia in adults. The pancreas is given unusual prominence as a cause of indigestion, and the tests of its dysfunction are clearly presented. A chapter on the simulation of gastro-intestinal disease by outside disturbances is well done, as is also the final chapter on practical dietetics.

The author is a young man connected with the Medical Faculty of the Egyptian University who has just completed a three years' study of disease of the digestive tract in London and on the Continent. His opportunities have been exceptional in allowing him to work in close association with Dr. A. F. Hurst and with several prominent German and Viennese clinicians; at the same time (in spite of his reference to Rehfuss as of Chicago) he has apparently made himself quite familiar with the American literature. His book, in consequence, gives the impression of having been written by one with a broad and seasoned viewpoint. It is to be regretted that more young men of promise cannot be given such opportunities for prolonged study in clinics outside their own country.

T. M.

ARTERIOSCLEROSIS. A Publication of The Josiah Macy, Jr., Foundation. By various contributors. Edited by EDMUND V. COWDRY, Washington University, St. Louis. Pp. 617; 86 illustrations. New York: The Macmillan Company, 1933. Price, $5.

THIS survey was prepared at the invitation of The Macy Foundation in order: "(1) to determine the data concerning arteriosclerosis which can be regarded as established and their relation one to another; (2) to discover and to definitely formulate the principal problems awaiting solution; and (3) to suggest the best means of attacking them." The need for a comprehensive survey of this complex problem by the best minds available is not only apparent in the size and scope of the resulting volume, but also becomes emphasized to the reader the further he progresses through the book. Though preliminary copies of some of the manuscripts were circulated to the contributors, they seem to agree chiefly on one fact, that most phases of the problem remain obscure and much must be discovered before theories of etiology, pathogenesis and therapy can be agreed upon and generally accepted. The inconsistencies, then, that are found in various chapters are to be expected, perhaps even welcomed as stimulating; but one would think that at least the ground to be covered by the title could have been agreed upon in advance. Thus some include syphilis and other infections and the changes following functional disuse, while others exclude them by definition. Satisfying is Anitschkow's chapter on Experimental Arteriosclerosis; he is so confident that cholesterol is the *materia peccans*. To be sure, he admits that there must be other factors, but of these we get little information, just as we are told but little more by those who unite the condition with the inevitability of the aging process. Then the reader's confidence in the rôle of cholesterol is rudely shaken in the very next and one of the most interesting chapters, by H. G. Wells on the Chemistry of Arteriosclerosis. Here we learn that "The disorganization of arterial walls with advancing age presents features which seem to indicate that this is, primarily, only the natural behavior of colloidal membranes," as "the changes that take place in senile arteriosclerosis show a striking agreement with the well-known behavior of aging colloids." With the aging of a colloidal gel, the particles become less dispersed with a reduced capacity to hold water. Elasticity is decreased and the gel tends to become granular with loss of colloidal properties. Increase of connective tissue and decrease of blood supply establish a vicious circle. Lipoids and calcium salts being nearest the saturation point are easily deposited, *i. e.*, these are secondary changes

only. MacCallum finds "but little evidence in favor of the idea that infections, whether acute or chronic, play a great part in the pathogenesis of arteriosclerosis;" whereas Cobb "suggests that infections and exogenous toxins which cause encephalitis or encephalopathy may also cause arteriosclerosis." In the chapter on Hypertension, Lange states his belief that functional changes come first and that the structural changes are due to the hypertonia; yet Bell emphasizes that structural changes are known to take place before a significant rise in pressure occurs. However, such differences are inevitable in the present state of our knowledge, and are much preferable to an easy, unwarranted, dogmatic unanimity.

Other chapters are: The Development of Our Knowledge of Arteriosclerosis (E. R. Long); The Structure and Physiology of Bloodvessels (E. V. Cowdry); Physical Properties of Arteries in Health and Disease (C. Bramwell); Mineral Constituents of Bloodvessels as Determined by the Technique of Micro-incineration (A. Policard); Statistical Study of Arteriosclerosis (E. Sydenstricker); Arteriosclerosis in Lower Mammals and Birds: Its Relation to the Disease in Man (H. Fox); Race and Climate as Possible Factors (P. Stocks); Nutrition in Relation to Arteriosclerosis (G. R. Minot); The Pathogenesis of Arteriosclerosis (W. Ophüls); Retinal Arteriosclerosis (J. S. Friedenwald); Coronary Arteriosclerosis (H. T. Karsner); Sclerosis of the Pulmonary Arteries (H. T. Karsner); Hereditary Aspects of Arterial Hypertension in Relation to Arteriosclerosis (G. D. Williams, who accepts that there is an hereditary disposition to hypertension). For a further critique and abstract of the body of the book, the reader is referred to Dr. A. E. Cohn's Summary in the last chapter, which incidentally cannot but emphasize further the complexity of the problem and the value of the various contributions, even in their contradictory interrelations.

E. K.

THE THYROID GLAND: ITS CHEMISTRY AND PHYSIOLOGY. By CHARLES ROBERT HARINGTON, M.A., PH.D., F.R.S., Professor of Pathologic Chemistry, University of London. Pp. 222; 28 illustrations and 14 tables. London: Oxford University Press, 1933. Price, $4.50.

THIS excellent monograph may be recommended unhesitatingly to those desiring a critical and complete summary of the modern knowledge of the thyroid gland from the standpoint of the chemist and physiologist.

The author who, with his teacher, George Barger, to whom the book is dedicated, is responsible for the achievement of the synthesis of thyroxin, writes from first-hand knowledge when he discusses in detail the chemistry of various active compounds which have been isolated from the thyroid. Of particular interest are the recent findings which indicate that both thyroxin and di-iodotyrosin are constituents of the thyroid gland protein, thyreoglobulin. The thyroxin, when in the gland (before chemical hydrolysis), is most probably present in peptid linkage with other amino acids. When administered by mouth, peptids of thyroxin (synthetic derivatives of thyroxin and an amino acid) exert a marked influence upon basal metabolism, whereas pure thyroxin is relatively inert.

The monograph is replete with the historical aspects of the subject, with many citations from ancient sources. The operative treatment of goiter was practised as early as 30 A.D., while burnt sponge (a source of iodin) was administered therapeutically in the thirteenth century. The use of iodin in solution in potassium iodid was initiated by Coindet, a Geneva physician, in 1819.

The book ends with the following paragraph: "The urgent need (for an explanation of the etiology of Graves' disease) is manifest. Graves' disease constitutes the outstanding problem in connection with the thyroid, and

the present situation, in which the only practical means of handling the condition consists of a palliative surgical measure devoid of any rational basis, remains a reproach to all who are interested in the physiology of the thyroid gland." The Reviewer does not feel that these words imply a criticism of the surgeon. It indicates a line of progress which may follow from further research, which may spring from foundations of knowledge already laid and adequately dealt with in the monograph.

D. D.

THE HISTORY AND EPIDEMIOLOGY OF SYPHILIS. The Gehrmann Lectures, University of Illinois, 1933. By WILLIAM ALLEN PUSEY, A.M., M.D., LL.D., Professor of Dermatology Emeritus, University of Illinois; sometime President of the American Dermatological Association and of the American Medical Association. Pp. 113; 37 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, $2.

IN the first of the three lectures—The Beginning of Syphilis—a strong and up-to-date presentation of the Columbian origin of syphilis in Europe is given. The lecture might well have been so entitled, because its pre-Columbian origin in this continent is not explored. Much is made of Haustein's recent article (1930) and the often fantastic accounts of Oviedo and Diaz de Isla are taken as quite valid. It is unfortunate, both for the greater interest and for the sake of fairness, that the counter arguments of Sudhoff, Singer and other eminent believers in the existence of pre-Columbian syphilis in the eastern hemisphere were not taken into consideration. The second lecture—Development of Our Knowledge of Syphilis—portrays the gradual acquisition of knowledge of the disease from Dürer to Noguchi, chiefly following Prokosch for the earlier periods. Emphasis is given to John Hunter and "the confusion into which, through his great authority, the subject was thrown by his false views," and also to the great discoveries of the last 30 years. In the third lecture—The Epidemiology of Syphilis—treated more statistically than historically, are considered: the reservoir of infection, the infecting organism, the susceptible host, the means of transmission and the underlying principles of control. The book is well produced, as is customary from this press, with perhaps less than the usual number of typographic errors. Its chief defects are the incompleteness of the references and legends, and the, perhaps necessary, divorcement of illustrations from the text they illustrate.

E. K.

THE SCIENCE OF RADIOLOGY. By VARIOUS CONTRIBUTORS. Edited by OTTO GLASSER, Cleveland Clinic Foundation. Pp. 500; 108 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, $4.50.

THIS book, dealing with radiology in its broadest aspects, includes sections on industrial radiology, experimental radiology (especially in the realm of biology), ultraviolet and infra-red radiation, and recent discoveries in radiant energy (including the cosmic and Gurwitsch's rays). Each section is written by an authority in his particular field. The book is designed to give a "proper perspective to and appreciation of the historic foundation of radiology" and is, therefore, fundamentally historical in its approach. Its scope is much wider than this, however. Beginning with Roentgen's discovery, it traces the development of radiology until it finally deals extensively with radiation physics, dosimetry, modern appliances, and modern diagnostic and therapeutic methods. Though of interest chiefly to the radiologist, it will be useful to the clinician if he is interested in deriving the greatest possible aid from one of medicine's greatest diag-

nostic and therapeutic agents. Its exhaustive bibliography makes it a useful reference and source book. The younger radiologist will find it of value in giving him the historic background of the great science as it is known today. It is a brilliant contribution to medical history and practice.

E. P.

Red Blood Cell Diameters. By Cecil Price-Jones, M.B. (Lond.). Pp. 82; 44 illustrations. New York: Oxford University Press, 1933. Price, $3.50.

The size of erythrocytes, whether expressed in diameters or volumes, has in recent years become a matter of increasing theoretical and practical interest. In this small book, the author, the leading exponent of the dry method of measuring blood cell diameters, has collected, expanded and improved his contributions to the subject, reprints being no longer available. The statistical method of treatment, given in clear, simple style, here forms an adequate basis for accepting the average diameter of 7.2 μ of human erythrocytes by this method (92 normal men, 8 women); also for the establishment of the diurnal variation, increase in pernicious anemia, emphysema, etc. The values after hemorrhage are admittedly based on too few cases to be accepted as standards.

E. K.

Medicine in Canada. By William B. Howell, M.D., Anesthetist-in-Charge, Royal Victoria Hospital; Lecturer in Anesthesia, McGill University, Montreal. Vol. IX of Clio Medica. Pp. 137; 6 illustrations. New York: Paul B. Hoeber, Inc., 1933. Price, $1.50.

This little volume is the ninth in a series of small handbooks on the history of medicine appearing under the general title of "Clio Medica." In concise and very readable form, and with frequent touches of humor, the author presents brief sketches of some of the early pioneers of Canadian medicine, as well as outlining the origins and growth of the more eminent medical schools. A reading of the book reveals so much in the way of anecdote, and so well does the author continue to illuminate the background of the period, that it can hardly fail to appeal to any reader, no matter how remote may be his interest in medicine. In common with the rest of the series, the small size of this book should recommend it particularly to the busy practitioner who must allow himself only a limited time with his books.

N. McL.

BOOKS RECEIVED.

NEW BOOKS.

The Surgical Clinics of North America. Volume 13, No. 5 (Chicago Number, October, 1933). Pp. 254; 93 illustrations. Philadelphia: W. B. Saunders Company, 1933.

Nature and Nuture. By Launcelot Hogben, M.A., D.Sc., Professor of Social Biology in the University of London. Pp. 143. New York: W. W. Norton & Co., Inc. Price, $2.75.

Speech Disorders. A Psychological Study of the Various Defects of Speech. By Sara M. Stinchfield, Ph.D., formerly Associate Professor in Psychology, Mount Holyoke College; Lecturer in Psychology, University College, University of Southern California Speech Clinic, Orthopædic Hospital School, Los Angeles. Pp. 341; 8 plates of illustrations. New York: Harcourt, Brace & Co., 1933. Price, $4.00.

New Introductory Lectures on Psychoanalysis. By SIGMUND FREUD, M.D., LL.D. Translated by W. J. H. SPROTT. Pp. 257; 1 illustration. New York: W. W. Norton & Co., Inc., 1933. Price, $3.00.

Maternal Mortality in New York City. A Study of All Puerperal Deaths, 1930–1932. By the New York Academy of Medicine Committee on Public Health Relations. RANSOM S. HOOKER, M.D., F.A.C.S., Director of the Study. Pp. 290; 89 tables. New York: The Commonwealth Fund, 1933. Price, $2.00.

The Bristol Medico-Chirurgical Journal, Special Jubilee Number, Vol. 50. Editor: J. A. NIXON, C.M.G., M.D., F.R.C.P. Pp. 198; illustrated. Bristol: J. W. Arrowsmith, Ltd., 1933. Price, 3s.

The coincidence of the centennial of the Bristol Medical School with the semi-centennial of the Journal has given rise to this special number which constitutes a valuable record of Bristol medicine. It contains illustrated historical articles on the Journal and the school, and on Bristol's contributions to medical progress.

Arritmias (Estudio Semilógico). By DR. ANTONIO BATTRO. Pp. 246; 141 illustrations. Buenos Aires: "El Ateneo," 1933.

The Medical Clinics of North America, Volume 17, No. 3 (Philadelphia Number, November, 1933). Pp. 326; 59 illustrations. Philadelphia: W. B. Saunders Company, 1933.

The Cortical Localisation of Cerebral Function. By PROFESSOR J. SHAW BOLTON, M.D., D.Sc., F.R.C.P. The Henderson Trust Lectures, No. XII. Pp. 23; 23 illustrations. Edinburgh: Oliver & Boyd, 1933. Price, 6d.

Rose Research on Lymphadenoma. By Various Contributors. Pp. 136; 98 illustrations, many in color. Baltimore: William Wood & Co., 1933. Price, $7.25.

International Clinics. Volume IV, Forty-third Series, 1933. By Various Contributors. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore. Pp. 317; 56 illustrations, 3 in color. Philadelphia, J. B. Lippincott Company, 1933.

I Reumatismi Cronici. By DOTT. RICCARDO ARRIGONI. Pp. 344; illustrated. Pisa: Casa Editrice U. Giardini, 1933–XI.

A Theory of the Formation of Animals. By W. T. HILLIER, M.R.C.S., L.R.C.P. Pp. 166; 98 text illustrations and 7 full-page plates. Baltimore: William Wood & Co., 1933. Price, $3.00.

The Genius of Louis Pasteur. By PIERS COMPTON. Pp. 361; illustrated. New York: The Macmillan Company, 1932. Price, $4.50.

Red Medicine: Socialized Health in Soviet Russia. By SIR ARTHUR NEWSHOLME, M.C.B., M.D., formerly Principal Medical Officer of the Local Government Board of England and Wales; and JOHN ADAMS KINGSBURY, LL.D., Secretary of the Milbank Memorial Fund, formerly Commissioner of Public Charities, City of New York. Pp. 324; illustrated. Garden City, N. Y.: Doubleday, Doran & Co., Inc., 1933. Price, $2.50.

NEW EDITIONS.

Voluntary Motherhood. By ANTOINETTE F. KONIKOW, M.D. Pp. 36; 8 illustrations. Fourth edition. Boston: Buchholz Publishing Company, 1933.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY.

UNDER THE CHARGE OF
I. S. RAVDIN, B.S., M.D.,
J. WILLIAM WHITE PROFESSOR OF SURGICAL RESEARCH, UNIVERSITY OF PENNSYLVANIA,
AND
C. G. JOHNSTON, M.S., M.D.,
INSTRUCTOR IN SURGERY, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA, PA.

RECENT ADVANCES IN PRE- AND POSTOPERATIVE TREATMENT.

DURING recent years, the increasing importance of physiological chemistry and physiology in medical training has been reflected in the practice of surgery. Technical advances in surgery have in the last five years been of relatively less importance than the tremendous advances in the pre-operative and postoperative treatment of the patient. The hit-or-miss administration of fluids, salts and glucose by one or another method has given way to more accurate estimation of the needs of the patient. Light is beginning to dawn on the vexing problem of postoperative pulmonary complications. It is because we believe that it is by attention to the details of treatment of the individual patient as much as by the operation itself that mortality and morbidity can be minimized that we have chosen this subject for review.

Abdominal Distention.—The importance of distention on the dynamics of the intestinal activity, respiration and circulation has been well pointed out during the past year.

The factor which distention plays in obstruction has been reviewed by HERRIN and MEEK (*Arch. Int. Med.*, 1933, **51**, 152). VAN ZWALENBURG (*Ann. Surg.*, 1907, **46**, 780) had shown that an intra-intestinal pressure of 90 mm. of mercury delayed the blood flow of the intestinal vessels, while a pressure of 130 mm. of mercury stopped it entirely. DRAGSTEDT, LANG and MILLET (*Arch. Surg.*, 1929, **18**, 2257) found that the duodenum, jejunum and ileum were sensitive to increases in the intestinal pressure in that order, an intrajejunal pressure of 80 mm. of mercury reducing the jejunal blood flow by about 60%. RAINE

and PERRY (*Arch. Surg.*, 1929, **19**, 478) came to the conclusion that distention in rabbits increased intestinal peristalsis and secretion and diminished reabsorption. BURGET and his associates (*Arch. Surg.*, 1930, **21**, 829; *Arch. Int. Med.*, 1931, **47**, 593) have shown in isolated intestinal loops distention results in vomiting, anorexia, and finally rupture of the loop and peritonitis, while these factors are not initiated as long as the distention of the loop is prevented.

HERRIN and MEEK (*Arch. Int. Med.*, 1933, **51**, 152), attempting to explain the symptoms and fatal outcome which follow intestinal distention, found that mechanical distention of loops completely separated from the continuity of the gastro-intestinal tract resulted first in a depression of activity, retching, loss of appetite, vomiting, rapid pulse and death. There occurred also a decrease in the chlorid concentration, a loss of plasma and a rise in the non-protein nitrogen. The hemoglobin increased considerably and, as a rule, there was a moderate increase in the alkali reserve.

WANGENSTEEN and his associates (*Arch. Surg.*, 1933, **26**, 933; *West. J. Surg.*, 1932, **40**, 1; *Minnesota Med.*, 1933, **16**, 96; *J. Am. Med. Assn.*, 1933, **100**, 1910) have called attention to the valuable aid which suction siphonage through a nasal catheter affords in the treatment of lesions associated with intestinal distention. The authors are careful not to advise suction siphonage in strangulation obstruction, but in adhesive types of obstruction, in postoperative ileus and in acute gastric dilatations, the method has proved to be of real therapeutic value. In mechanical obstruction unassociated with gangrene it permits the surgeon to take time properly to evaluate the condition of the patient, to restore the fluid and salt balance and to relieve the strain placed on the circulation and respiration due to the marked increase in the intra-abdominal pressure. Wangensteen has pointed out that it is important to administer fluids either subcutaneously or intravenously during the period that the suction siphonage is being used.

Abdominal pain usually disappears with the decompression of the stomach and intestines. Borborygmi may be heard on auscultation, but they are not as violent or as frequent as before the institution of suction drainage. The only obstructions of a non-gangrenous character in which Wangensteen believes suction drainage to be contraindicated are those of the sigmoid.

We have recently used this method in a series of patients with very satisfactory results and are convinced that it is a definite advance in the treatment of the distended gut.

PLUMIER (*Arch. int. de physiol.*, 1909, **8**, 1), THORINGTON and SCHMIDT (AM. J. MED. SCI., 1923, **165**, 880), FREY (*Ztschr. f. d. ges. exp. Med.*, 1923, **31**, 49), DIMITRENKO (*Am. J. Physiol.*, 1924, **68**, 280), MCIVER (*Ann. Surg.*, 1927, **85**, 704) and RUNGE (*Arch. f. Gynäk.*, 1924, **122**, 142) have studied the effect of increasing the abdominal pressure on the arterial or venous pressures or both. Thus Thorington and Schmidt showed that marked increase in the intra-abdominal pressure so influenced the circulation of the kidney as to seriously reduce the renal excretion.

More recently, BRAMS, KATZ and KOHN (*Am. J. Physiol.*, 1933, **104**, 120) have reported the effect of abdominal distention and release on the blood pressure in the carotid artery and the veins above and

below the diaphragm. They have shown that rapid or even gradual increases in the intra-abdominal tension may profoundly affect the dynamics of the circulation. After the release of marked abdominal distention, which had persisted for some time, the fall in the arterial pressure was as much as 40 mm. of mercury. They wisely caution that such a drop "in a feeble patient may result in death." McLAUGHLIN and LEVERING (to be published) have shown that rapid increases or releases in the intragastric pressure, which has been maintained for even a short period, result in profound changes in the arterial and venous pressures; in fact, tamponade of the abdominal aorta can be accomplished by increasing the intragastric tension sufficiently.

BEECHER (*J. Clin. Invest.*, 1933, **12**, 639) has measured the effect of laparotomy on the respiration. It is, of course, well known that distention decreases the pulmonary ventilation. In 1927, CHURCHILL and McNEIL (*Surg., Gynec. and Obst.*, 1927, **44**, 483) described a marked reduction of the vital capacity following abdominal operations. PASTEUR (*Lancet*, 1908, **2**, 1351), MULLER, OVERHOLT and PENDERGRASS (*Arch. Surg.*, 1929, **19**, 1322), PATEY (*Brit. J. Surg.*, 1929, **17**, 487) and others have shown that after abdominal operations there is a limitation of the motion of the diaphragm. OVERHOLT (*Arch. Surg.*, 1930, **21**, 1282) found the normal pressure within the peritoneal cleft to be below the atmospheric pressure. Abdominal incision increased this pressure and the resulting pneumoperitoneum resulted in pulmonary subventilation. These findings have been verified by PRINZMETAL, BRILL and LEAKE (*Surg., Gynec. and Obst.*, 1933, **56**, 129).

Beecher found that laparotomy profoundly affects respiration by (1) markedly reducing the tidal air, and by (2) markedly increasing the respiratory rate. The rapid, shallow type of respiration sets up a vicious cycle, tending to increase further the respiratory rate. There was a great reduction in complemental air, greater following upper than lower abdominal operations in both men and women. The reduction in supplemental air was greater following upper than lower abdominal operations in men, but not in women. There was a marked reduction in the vital capacity. Beecher concluded that the differences after upper and lower abdominal operations and in men and women were comparatively small, yet there are large differences in the morbidity of pulmonary complications in the four groups. There are undoubtedly other factors concerned in the etiology of postoperative pulmonary complications which have not as yet been measured accurately.

The Blood Count in Infection.—The revival of interest which began with the studies of the Arneth count of nuclear lobulations of the neutrophilic leukocyte has found numerous surgical applications. FITZ-HUGH'S (*Int. Surg. Dig.*, 1933, **15**, 195) excellent review of this subject has been drawn on by us extensively.

The original method of ARNETH (*Deutsch. med. Wchnschr.*, 1904, **30**, 54) has been largely replaced in this country by simplifications, such as the Schilling hemogram (The C. V. Mosby Company, 1929), the Piney count (P. Blakiston's Son & Co., 1927), Cook's polynuclear count (Gilmour and Lawrence, 1914), Farley's non-filament neutrophil count (AM. J. MED. SCI., 1930, **180**, 336) and several others.

Fitz-Hugh very aptly states that "The cytoplasmic evidence of immaturity (basophilia, basic granulation, etc.) do not always go hand

in hand with nuclear evidences of immaturity (non-segmentation, loose chromatin structure, etc.). Degenerative and toxic changes in the neutrophils may simulate those of immaturity and, in addition, may render difficult the objective classification of cells seen. Small lymphocytes with unusual 'azure granulation' may be mistaken for young metamyelocytes. Monocytes (of 'transition type') may be mistaken for 'band forms' and *vice versa*. The differentiation of 'filament' or 'truly lobulated' nuclear from the 'pseudolobulated' non-filament nuclear is not always easy. These morphologic and technical difficulties are not important sources of error in the hands of experienced workers, but may invalidate the reports of the uninstructed or careless observer."

Fitz-Hugh feels that in themselves these tests are of little or no diagnostic importance, since infection is not the only cause of a "shift to the left." He does not believe that the surgeon can depend on the "neutrophilic shift" to differentiate between acute cystic duct obstruction with infection and acute coronary thrombosis. Non-infective visceral disorders may cause a "shift to the left," as well as internal hemorrhage, apoplexy, paroxysmal tachycardia, diabetic and uremic coma. At times, infection, which is quite marked, may be associated with little or no shift. Nor can the magnitude of the shift be depended upon for any definite prognostic importance.

While numerous observers state that a non-filament count of 40 per cent or more is in itself a grave prognostic omen, Fitz-Hugh does not believe this. Furthermore, he has not even been impressed with the concept that a progressive daily increase in the "shift to the left" is always of grave significance, as that is often demonstrable in pneumonia. The value of a properly performed and repeated study of the neutrophils is only that it is a worth while adjunct to other methods of clinical study. Taken in this way the information may be of critical importance.

Luck (*Am. J. Surg.*, 1933, **19**, 375), in a study of the Schilling hemogram in acute appendicitis, reports the sequence of events as follows: (1) Mobilization of available mature leukocytes. (2) Liberation of immature forms of neutrophils into the blood stream: (*a*) Increase in stab forms of a degenerative type, (*b*) appearance of juvenile forms, and (*c*) appearance of myelocytes. (3) Decrease in, or absence of, eosinophils. (4) Decrease in lymphocytes and monocytes. The extent of liberation of immature forms of neutrophils, "the shift to the left," depends on the severity of the infection. Myelocytes appear only in cases of most severe infection, and usually in appendicitis this means peritonitis has developed. If the acute attack subsides, either with or without surgery, there usually occurs first an increase in monocytes, following which immature neutrophils disappear, the segmented type approaches normal in count, and the lymphocytes rise, while eosinophils appear.

Luck regards the Schilling count as a very valuable aid in tracing the course of acute appendicitis, and also as a means of differentiating appendicitis (or infections) from conditions in which a high leukocyte count is unaccompanied by the presence of immature neutrophils (indicative of absence of infection).

Harter and Lyons (*Surg., Gynec. and Obst.*, 1933, **56**, 182) have also studied the surgical applications of the Schilling count. They

believe it is of more value than the routine Ehrlich differential count in detecting the degree and persistence of the infection. Reznikoff (*J. Am. Med. Assn.*, 1929, **93**, 963) believes that changes in the hemogram may antedate clinical symptoms.

The Effect of Drugs on Intestinal Activity.—From time to time the clinician has been confronted with the problem of which drug to use in obtaining certain actions in the gastro-intestinal tract. Of major interest to the surgeon is the action of opium and its derivatives. As early as 1840, Alonzo Clark advocated the use of large doses of opium in the treatment of peritonitis, and since that time this drug has played a prominent rôle in the therapy of the disease.

Plant and Miller (*J. Pharm. and Exp. Therap.*, 1926, **27**, 361; 1928, **32**, 437), and Gruber and Robinson (*Ibid.*, 1929, **37**, 101) have shown that morphin has a stimulating effect on the smooth muscle of the bowel. Plant and Miller found that morphin caused an increase in intestinal tonus and an increase in the amplitude of the peristaltic activity of the small intestine. Dvorak and his associates (*Proc. Soc. Exp. Biol. and Med.*, 1931, **28**, 434) confirmed these observations. Reid (*Ibid.*, 1931, **29**, 220) found that while morphin increased the tone and rhythmic activity, it did not increase the propulsive power of the intestine.

Roentgenologists have long recognized that opium causes a retardation in the passage of a barium meal, and certain observers (Macht: Am. J. Med. Sci., 1917, **154**, 874) have stated that this is due to the spastic effect of opium on the sphincters of the gastro-intestinal tract, while others believe that the entire gut is put at rest by the arrest of peristalsis.

More recently Orr (*Ann. Surg.*, 1933, **98**, 835) has found that morphin in therapeutic doses increases the tone of the small intestine, the amplitude of segmentation movements and initiated peristaltic waves in the dog. Large doses abolished the peristaltic action, while very large doses increased the amplitude of the rhythmic segmentation contractions. Orr called attention to the fact that distention of the small bowel was a dreaded feature of peritonitis. He believes that any drug which will relax or splint the distended bowel, and thus prevent intestinal motility, is based on illogical foundations. However, since morphin stimulates bowel tone and rhythmic contractions, its use in peritonitis is founded upon good basic principles, although these were at first not recognized. The action of morphin on the intestine persists for approximately 6 hours. Its use in preventing the overdistention of the small intestine in peritonitis, intestinal obstruction and paralytic ileus is thus indicated.

Ochsner and Gage (*Am. J. Surg.*, 1933, **20**, 378), in a study of adynamic ileus, have reviewed the action of various substances on the bowel. These authors also have found morphin to be of definite value in the prevention and treatment of adynamic ileus. They found that glucose given intravenously results in a decrease in the intestinal motility, while if sufficient insulin is given with the glucose, the inhibiting effect is not nearly so marked. Hypertonic Hartman's solution, on the other hand, when given intravenously, results in a marked increase in the intestinal tone and an associated increase in the intestinal movement.

In 1924, HUGHSON and SCARFF (*Bull. Johns Hopkins Hosp.*, 1924, **35**, 197) reported that the intravenous administration of hypertonic sodium chlorid increased the intestinal activity. These observations have now been amply confirmed by many observers. Ochsner and Gage believe that the intravenous administration of solutions containing calcium and potassium chlorid are more efficacious in stimulating intestinal activity than are solutions containing sodium chlorid alone. In our own laboratory we have found other calcium salts to be quite as efficacious as the chlorid.

Fluid and Salt Balance.—Last year, we reviewed a part of the literature dealing with this subject so that it will not be covered anew. We wish, however, to mention the paper of DRAKE, MARSH and GAMBLE (*Am. J. Dis. Child.*, 1930, **40**, 709), wherein it is pointed out that where changes in blood reaction are associated with changes in the fluid balance it is of greater importance to correct the dehydration than the blood reaction. In fact, in correcting the dehydration the blood reaction may in itself be restored to normal. A small loss of base is not in itself important. Where ketosis is present together with dehydration, glucose should be used with sodium chlorid. We have amply confirmed the fact that in dehydration associated with a change in the blood reaction in either direction, as seen in surgical practice, solutions of sodium chlorid and glucose provide the only substances that are vitally necessary.

JONES and EATON (*Arch. Surg.*, 1933, **27**, 159) have very recently studied the problem of postoperative nutritional edema. When excessive amounts of water or sodium chlorid are given to a patient with a lowered serum protein, edema may result. WEECH and LING (*J. Clin. Invest.*, 1931, **10**, 869) have provided a fairly complete bibliography on the subject. Though but little attention has been given the subject by surgical investigators, Jones and Eaton have presented evidence that nutritional edema is not uncommonly associated with surgical procedures, particularly of the gastro-intestinal tract. They present data on 34 patients who developed a critically low amount of serum protein following routine surgical procedures. In most of these, some edema was present. Most of the low values for the serum protein were, they believe, the result of undernutrition, and the reduction in the intake of protein is, in their opinion, the most important element in the pathogenesis of the edema. The additional factors which influence the edema may be the administration of excessive amounts of fluid and salt after operation, profuse surgical drainage, sepsis, the loss of protein by massive hemorrhage and a retention of base associated with a temporary disturbance of renal function.

At times, edema may occur even though the serum protein may be within apparently normal values. In the very poorly nourished patient, Jones and Eaton believe that edema of the intestinal wall may result in a poorly functioning gastroenterostomy, and they suggest preliminary jejunostomy in patients who are obviously undernourished.

In 1921, MILLER and WILLIAMS (AM. J. MED. SCI., 1921, **161**, 327) studied the effect on the blood pressure and the non-protein nitrogen in the blood of excessive fluid intake. Later WEIR, LARSON and ROWNTREE (*Arch. Int. Med.*, 1922, **29**, 306) and ROWNTREE (*Ibid.*

1923, **32**, 157; *J. Pharm. and Exp. Therap.*, 1926, **29**, 135) reported on the intoxication of excessive fluid intake and found that intravenous salt solution prevented as well as cured this syndrome of water intoxication.

In 1923, Moss (*Proc. Roy. Soc. Lond.*, Ser. B, 1923–1924, **95**, 181) reported his observations on miner's cramp. In the colliers, he found that the excessive sweating resulted in the loss of very large amounts of chlorid and that the cramps could be relieved by the administration of sodium chlorid.

In the studies of Smyth, Deamer and Phatak (*J. Clin. Invest.*, 1933, **12**, 55) of so-called water intoxication, it was found that neither water retention in the body nor hemodilution is its most important feature. The convulsive symptoms are associated more closely with the loss of chlorid by way of the gastric secretion and a resulting alkalosis. They found little evidence that non-electrolytes increase in the blood to compensate osmotically the electrolyte depletion.

The Healing of Tissues.—Since the very important contributions of Harvey and his associates on the tensile strength of wounds and bones after fracture, surgeons have again found this field a fruitful one for investigation.

Howes, Briggs, Shea and Harvey (*Arch. Surg.*, 1933, **27**, 846) have studied the effect of complete and partial starvation on the rate of fibroplasia in the healing wound. They found that the healing strength in wounds of the stomach in adult rats was not appreciably affected by complete starvation. It was also not affected when only one-half the required amount of an adequate diet was given over a short period of time. On the other hand, when such a ration was continued over a long period, the rate of healing of the stomach wound was definitely retarded. This they believe to be due to a reduction, either separately or in combination, of certain dietary elements, probably the vitamins, especially in relation to the deficiency of salts and proteins. The study demonstrated that marked variations of the diet for short periods had little effect on the ability of wounds of the stomach of adult animals to heal.

Howes (*Surg. Gynec. and Obstet.*, 1933, **57**, 309) studied the strength of wounds sutured with catgut and silk. He found that in experimental wounds of the stomach of the rat sutured with catgut and silk of the same and different sizes, wounds which were repaired with silk showed earlier fibroplasia and the wounds accumulated strength more rapidly than those sutured with catgut.

Microscopic sections of the wounds showed the exudative phase to be of shorter duration in the wounds sutured with silk than in those sutured with catgut.

The experiments demonstrated that there was no advantage in using sutures of large dimensions. The observations as a whole are in accord with those of Halsted published some years ago.

Morton and Stabbins (*Ann. Surg.*, 1927, **86**, 430) and Pearse and Morton (*J. Bone and Joint Surg.*, 1930, **12**, 97) have reported on the circulatory factors influencing osteogenesis. The latter found that venous stasis in the region of an experimental bone defect of the fibula resulted in accelerated repair, earlier calcification and earlier union. In the paper by Morton and Stabbins, venous ligation was stated to

have given results which were in certain particulars diametrically opposed to the results obtained later by Pearse and Morton.

Recently, KEY and WALTER (*Arch. Surg.*, 1933, **27**, 935) have repeated the above experiments and have not been able to confirm either of the above observations in that "ligation of the veins around the elbow caused venous congestion in the foreleg and foot of the dog, but had no effect on the healing of a fracture or of a defect in the ulna."

Shock.—The number of papers on this subject that have appeared recently is ample proof of the fact that as yet the solution of this problem is not at hand. MOON and KENNEDY (*Arch. Path.*, 1932, **14**, 360), in a study of the pathology of shock, state that the syndrome is accompanied by gross and microscopic changes opposite in character to those produced by hemorrhage. These changes include dilatation and engorgement of the capillaries and venules, increased permeability of the capillary walls, and frequently effusion into serous cavities. Since barbital produces changes similar to those observed in shock, drugs having such properties are not advised when normal blood pressure and capillary tonus are important.

The trend within recent years has been to consider shock as due to a loss of blood into tissues outside of the vascular system. BLALOCK and his associates (*Arch. Surg.*, 1927, **15**, 762; 1930, **20**, 959; 1931, **22**, 314, 598, 610; 1929, **19**, 725. *J. Am. Med. Assn.*, 1931, **97**, 1794. *Arch. Surg.*, 1931, **22**, 638, and **23**, 848) have shown that trauma is an important factor in the loss of plasma into the tissues. PARSONS and PHEMISTER'S (*Surg., Gynec. and Obst.*, 1930, **51**, 196) observations confirm those of Blalock and his associates. ROBINSON and PARSONS (*Arch. Path.*, 1931, **12**, 869) compared the water content of the blood and muscles under a variety of conditions. After hemorrhage, the muscles lost and the blood gained in water content. Following histamin, the muscles gained and blood lost water. After trauma, there occurred a transfer of water from the blood to the muscles.

RUKSTINAT (*Arch. Path.*, 1932, **14**, 378), in an extensive general review of experimental traumatic shock, concludes that most of the features of shock can be produced experimentally by bleeding an animal (Moon and Kennedy would not agree with this) or by allowing blood to escape into traumatized tissues. After hemorrhage and in shock, the increased blood nitrogen and the decreased alkali reserve seem dependent on a decreased volume flow of blood. The loss of plasma proteins is without doubt of considerable importance in the development of secondary shock. We believe that the terms primary and secondary shock are hardly worthy of use.

One of the most interesting contributions to the knowledge of shock is the work of FREEMAN, MORISON and SAWYER (*Am. J. Phys.*, 1933, **104**, 628). FREEMAN (*Ibid.*, 1933, **103**, 185) had shown that prolonged hyperactivity of the sympathetic resulted in a reduction of the blood volume. Later he and his associates found that acute dehydration stimulated medulliadrenal secretion and set up a vicious circle. The similarity between traumatic shock and dehydration was stressed in that both conditions are characterized by vasoconstriction and a slowing of the blood flow which leads to a reduction in the volume of the circulating blood.

Attention should also be called to the work of SWINGLE (*Science*, 1933, **77**, 58), who believed that a lack of adrenal hormone was a

definite factor in shock. Thus, this concept is directly opposed to the Freeman theory. Personal observations with Cortin in surgical shock leads the Reviewers to the opinion that the Swingle concept is very likely incorrect; but the controversy is not as yet a settled one.

In 1914, Frank Mann stated that "Despite the enormous amount of work which has been done on surgical shock, there is still among recent writers no general agreement as to the causes and nature of this condition." We hope that this statement may not as easily be repeated a year hence.

OPHTHALMOLOGY.

UNDER THE CHARGE OF
WILLIAM L. BENEDICT, M.D.,
HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.,
AND
H. P. WAGENER, M.D.,
ASSISTANT PROFESSOR OF OPHTHALMOLOGY, MAYO FOUNDATION, ROCHESTER, MINN.

NUTRITIONAL DISEASES AND THE EYE.

THE relation between certain diseases of the eye and food deficiencies was first established by the clinical observation of children with keratomalacia and night blindness.

Johannes Nepomuk Fischer mentions in his treatise on ophthalmology (published in 1846) a partial necrosis of the cornea, which from the description must be keratomalacia. According to OLAF BLEGVAD (*Am. J. Ophth.*, 1924, **7**, 89), the first minute description of the disease was given by Albrecht von Graefe in 1866. The disease is here called "Hornhautverschwarung" and was connected by von Graefe with encephalitis infantilis, described shortly before by Virchow. The first symptoms of xerophthalmus, xerosis conjunctivæ, were first described by Bitot in 1863. This description was based on 29 cases of xerosis conjunctivæ which appeared together with hemeralopia in children of a larger growth in a foundling hospital in Bordeaux. The origin of the disease was for a time erroneously considered as an infection with the Bacillus xerosis, described in 1880 by Calomiatti (Leber), Kuschbert, Neisser, Schleich, and Schultz, but later investigators are now of the opinion that it is due mostly to nutritional phenomena. The disease is produced in the eyes of animals when the animals are kept on a diet deficient in fat-soluble vitamin A. BLOCH (*Am. J. Dis. Child.*, 1931, **42**, 263), in 1914, demonstrated before the Danish Pediatric Society many cases of xerophthalmus which he regarded as a constitutional disease due to nutritional deficiency. He called attention to the inhibition of growth and a decrease of immunity as symptoms of this disease. Because of the early age of many of the children, he could demonstrate hemeralopia in only a few of them. He made the statement that "food deficiency may be the true cause of this lesion; whether the disease is connected with a lack of vitamin, I do not know." Shortly before and coinciding with these clinical investi-

gations into xerophthalmia, McCallum produced a similar lesion experimentally in young rats and demonstrated that the deficient substance was the vitamin A.

The experimental proof necessary to align xerosis of the conjunctiva and night blindness with the lack of vitamin A was furnished by Fridericia and Holm (*Am. J. Physiol.*, 1925, **73**, 63). They devised methods of estimating the amount of visual purple in the retina of rats before and after bleaching in light. This enabled them to note the difference in the rate of regeneration of the visual purple in animals starved of vitamin A as compared with control rats receiving an adequate diet.

Many clinical investigations had suggested a relation between xerosis of the conjunctiva and certain kinds of night blindness in human beings. The two diseases often occurred jointly, and this association was mentioned as early as 1863 by Bitot, who first described xerosis conjunctivæ. In the course of time, ophthalmologists generally accepted the view that the three ailments, keratomalacia, night blindness and xerosis conjunctivæ, were different degrees of the same disease. The symptom which occurs first and most frequently in human subjects who live on a diet deficient in the fat-soluble vitamin A is hemeralopia. In adults it will usually be the sole symptom. Pillat (*Arch. Ophth.*, 1929, **2**, 256) found xerophthalmia in adults in China. Among the same symptoms, the curious dryness and discoloration of the skin and hair and the multiple abscesses without inflammatory symptoms were noted. Delay in the regeneration of the visual purple would account for the observed clinical facts. Probably a raising of the light threshold of the whole retina occurs, the periphery of the retina containing more rods and visual purple retaining the relatively greater light sensitivity. According to the investigations of Holm (*Acta Ophth.*, 1929–1930, **7–8**, 146), the retina belongs to the parts of the body that are comparatively rich in vitamin A, since a daily loss of less than 0.75 g. (*i. e.*, corresponding to 0.08 to 0.1 g. of dry substance) is sufficient to induce optimal conditions of growth in xerophthalmic rats that are beginning to lose weight. This author concluded that vitamin A was concentrated in the anterior parts of the rods higher than in most any other part of the body, and examination of the retina of the hog by means of the color reaction of Rosenheim, and the feeding of experimental animals depleted of vitamin A, has shown the presence of this food factor in the tissue under consideration. The dried tissue representing 4% of the retina is decidedly richer in vitamin A than ordinary butter fat. (Yudkin: *Arch. Ophth.*, 1931, **6**, 510.)

In human beings a relation exists between xerophthalmus and a certain kind of night blindness; the night blindness often preceding the xerophthalmia. Some authors have suggested a relation of this kind of night blindness to a deficiency of A vitamin in the diet, but others have made observations suggesting a connection between night blindness and exposure of the eyes to intense light. If this kind of night blindness depends on a deficit in the function of the visual purple, identical with that observed in the rats starved from vitamin A, both of these views contain a part of the truth.

BLEGVAD (*Am. J. Ophth.*, 1924, **7**, 89) made numerous experiments on young rats and established the fact that xerophthalmia in rats is due primarily to the lack of fat-soluble vitamin A. In xerophthalmia of human beings, however, so many factors entered the question that the matter was much more complicated than in experiments on rats.

BLOCH (*Am. J. Dis. Child.*, 1924, **27**, 139) pointed out the lesions of the skin as further evidence that xerophthalmus was a constitutional disease. Infections afflicted 38% of 32 scorbutic children, whereas 80% of 86 children with xerophthalmia had infections. Among scorbutic children, the infections were mild; thus, there was only 1 case of pneumonia, and this patient was suffering with xerophthalmia in addition to scurvy. Among xerophthalmic patients, on the other hand, there were many severe infections: pneumonia in 15 cases, bronchitis in 12, otitis media in 13, pyelitis in 27 (30%), and pyodermia in 14. Among infants there is desquamation of the epithelial cells of the skin and the mucous membrane of the urinary tract, on observation concurred in by SPRUCE (*Ann. Dis. Child.*, 1931, **6**, 17) who found also a high incidence of cutaneous sepsis among the cases. Apart from this cutaneous sepsis there was no evidence of a lowered resistance to general infections among people living on a xerophthalmia-producing diet.

WOLBACH, (*J. Exp. Med.*, 1925, **42**, 753) called attention to the formation of keratinizing epithelium in the conjunctiva, ducts of Meibomian glands, cornea, Harderian gland and the lacrimal gland.

WRIGHT (*Brit. J. Ophth.*, 1922, **6**, 164) noticed the frequent association with affections of the alimentary canal, grave constitutional disturbances and marasmus.

A clinical application of the necessity of vitamin A in the diet was attempted by HESS, LEWIS and BARENBERG (*J. Am. Med. Assn.*, 1933, **101**, 657), who made inquiry in regard to the occurrence of night blindness throughout the United States. In their opinion night blindness is the most delicate indicator of a lack of vitamin A in the dietary; in fact, the most delicate indicator known in relation to any of the vitamins, for it gives evidence of a deficiency by a symptom that is particularly subjective occurring before the least pathologic change can be detected—indeed, before any abnormal changes are discernible by means of the ophthalmoscope. They have shown that small amounts of whole milk, or even of boiled milk, will cure xerophthalmus rapidly or dispel night blindness. No case of xerophthalmia has been reported as developing on whole milk given in moderate quantity. These investigators do not believe that the average child requires any supplement of vitamin A above what it receives in 24 ounces (750 cc.) of milk. This opinion is based partly on the experience that supplements of vitamin A, whether in the form of carotin, haliver oil, or cod-liver oil, have brought about no benefit in growth, nutrition or immunity to infection.

FRAZIER and HU (*Arch. Int. Med.*, 1931, **48**, 507) observed a group of patients in Peiping with respect to the sequence in which the various pathologic changes occurred in the skin, noting an excessive epithelial keratinization resulting in the mechanical occlusion of hair follicles

and sweat ducts, and in secondary degeneration of the sebaceous and sweat glands.

Aykroyd (*Trans. Ophth. Soc. United Kingdom*, 1930, **50**, 230) noted that the diets in a series of cases of hemeralopia were found to be obviously deficient in vitamin A, and that in some cases the disease had developed in less than a month after the patient had passed from a diet rich in vitamin A to one almost devoid of it. One case was interesting in that the patient had learned that dark glasses protected him from the disease, or that covering up one eye by day insured a useful eye for the dark. In women the disease is usually associated with pregnancy, tending, when untreated, to clear up spontaneously after delivery.

The deficiency of fat-soluble vitamin A in the organism may be produced in the following way: (1) By reduced doses of fat-soluble vitamin A from food poor in the substance or by a deficient absorption in the intestine; (2) by increased consumption during a rapid growth or a severe disease.

Although many of the symptoms of xerophthalmia and hemeralopia clear up on the addition of cod-liver oil to the diet, it is clear that the substance vitamin A is only one of the agencies needed to restore to normal the skin, eyes and digestive tract. The addition of thyroid extract and salts was used by Wright (*Brit. J. Ophth.*, 1922, **6**, 64) in treating cases of keratomalacia in southern India. The value of vitamin A as an agent working against infection has been tested by Cardell (*Brit. J. Ophth.*, 1930, **14**, 354) who used it in conjunction with ultraviolet light in phlyctenular ophthalmia, hordeola, episcleritis, corneal ulcers and tuberculous iritis with encouraging results. Crames (*Lancet*, 1930, **1**, 1153) on the contrary, says that vitamin A should not be called an anti-infectious vitamin.

The predominance of ocular symptoms in disease due to deficiency of vitamin A overshadows the effect of shortage of some other vitamin. The direct effect on experimental animals of deprivation of vitamin G is indicated by the findings of Day and O'Brien (*Am. J. Ophth.*, 1931, **14**, 1005) regarding the development of cataract in the eyes of rabbits.

In infantile scurvy, swelling of the upper lid and exophthalmus are caused by hemorrhage between the bone and the periorbita. The long bones undergo changes characteristic of scurvy and there may be bleeding from the gums. Hemorrhages are controlled and the exophthalmus will disappear if sufficient vitamin C is provided in the diet. With the taking of 3 ounces of orange juice daily, exophthalmus has disappeared in 4 days. Exophthalmus appears as a complication of scurvy only among infants. The average age of 22 patients in authentic cases collected by Dunnington (*Arch. Ophth.*, 1931, **6**, 731) was $10\frac{1}{2}$ months, the youngest being 7 months and the oldest 2 years of age.

In this country where there is no shortage of any necessary kind of food, the diseases incident to deficiency of any vitamin are associated with some other conditions such as carcinoma of the intestine or liver, and the severe cases of keratomalacia and night blindness are seen only in the extreme marasmus following some chronic debilitating disease. Bitot's spots on the conjunctiva may be seen in persons who have no

symptom of night blindness or of keratomalacia. From them Corynebacterium xerosis can be obtained in large numbers in a smear and grown profusely in culture. The only symptoms are dryness of the eyes and the undesirable white patches on the conjunctiva in the palpebral fissure. Ordinary antiseptic eye lotions are not effective in removing them.

It is quite doubtful if any of the human diseases as we see them in this country can be said to be due to lack of any one vitamin. The relation of vitamins A, B, D and G to the development of growth of the body as well as the maintenance of good skin, teeth, hair and eyes is evident in clinical and experimental observations. A clear explanation of the part each substance plays cannot be made on what evidence is available today.

In Bloch's early papers on the subject of xerophthalmia, he stated that the disease was due to a "deficiency of special lipoids, or lipoid elements." In 1931, he cites his statement made in 1914 and adds: "Since then, notwithstanding the arduous work of many prominent investigators, knowledge of this substance has not been extended beyond the fact that it is connected with certain lipoids." (BLOCH: *Am. J. Child.*, 1931, **42**, 263.)

In 1931, vitamin A was isolated by J. C. Drummond, of London, as one of the two products obtained by splitting carotene, the growth-promoting vitamin found in liver, cod liver oil, butter fat, egg yolk and green and yellow vegetables. At the same time, he reported that he had obtained from halibut-liver oil a sticky yellowish oil which is $\frac{9}{10}$ pure vitamin A.

Another group of diseases related to metabolism of lipoid are the xanthomatoses (Gaucher's disease, Niemann-Pick's disease, Hand-Schuller-Christian's disease, the xanthomas occurring in icterus, diabetes and pregnancy, and so-called essential xanthomatosis). ROWLAND (*Arch. Int. Med.*, 1928, **42**, 611) coined the term xanthomatosis and proved that Hand-Schuller-Christian's disease belonged in the same category with the other disturbances of metabolism of lipoid. It is a rare disease of children, due to a disturbance of lipoid metabolism and is characterized by deposits of lipoids, chiefly cholesterol and its esters, in various organs and tissues of the body. Among the chief symptoms are defects in bones, exophthalmus, diabetes insipidus, gingivitis, cessation of growth and occasionally adiposogenital dystrophy. SOSMAN (*J. Am. Med. Assn.*, 1931, **98**, 110) has collected 45 cases and speaks of other unreported cases. In this disease—essentially one of childhood—the exophthalmus often is an early sign. Roentgenograms reveal the defect in the bones of the skull made by deposit of lipoid substances and formation of a thick fluid which gives the characteristic cystic feeling on palpation. The bony lesions of the skull are similar to those of osteomyelitis as represented in the roentgenograms, and undoubtedly there is some confusion in the diagnosis. Surgical intervention has been of little benefit. Mild cases have been cured by application of radium and Roentgen rays applied over the affected bony areas. The defects in the bones are filled with new bone, thicker and more dense than the surrounding bone.

PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF DECEMBER 18, 1933.

Electrokinetic Studies on Marine Eggs.—Katsuma Dan (Zoölogical Laboratory, University of Pennsylvania). The method used in this study is that which was described elsewhere (*J. of Cell. and Comp. Physiol.*, 1933, **3**, 477). It consists in measuring the horizontal displacement from the vertical path of fall of eggs.

The following charges were found on eggs of various species under different circumstances.

1. Arbacia punctulata. Eggs with jelly, −34.1 millivolts; eggs without jelly, −30.3 millivolts. This egg, when killed by heat, does not change its charge at all, and when it is fertilized, the absolute magnitude of the charge is decreased.
2. Cumingia tellinoides. Eggs with jelly, −34.1 millivolts; without jelly −28.8 millivolts.
3. Asterias forbesii. With jelly, −18.95 millivolts; without jelly, −19.9 millivolts; eggs killed by heat, −19 millivolts.
4. Echinarachnius parma. With jelly, −31.6 millivolts; without jelly, −20 millivolts, approximately.
5. Nereis limbata. Unfertilized eggs, −10 millivolts, approximately.
6. Cerebratulus lacteus. Chorions containing eggs move toward the anode. Egg cells move toward the cathode within the chorions. However, these egg cells, when they are taken out into the sea-water, do not show any movement, thus indicating zero potential.

Comparative Antigenic Studies on Egg Albumin Denatured by Intense Audible Sound and By Other Means.—E. W. Flosdorf and L. A. Chambers (Laboratories of Bacteriology, Pediatrics and Medical Physics, University of Pennsylvania). It has previously been reported by the authors[1] that upon exposure to intense audible sound a variety of chemical changes can be induced, including that of rapid coagulation at 25° C. of well-dialyzed solutions of three times recrystallized egg-albumin.

Antigenic studies with the washed coagulum from treated albumin indicate an altered specificity and antigenic power similar to that produced by other means such as by heating in an alkaline or acid solution. The uncoagulated fraction retains the original specificity and antigenic power. The results of Wu, Tenbroeck and Li concerning the diminished antigenic power and altered specificity of denatured egg albumin were confirmed in this study insofar as it was necessary to reproduce them.

Long treatment with the sonic vibrator redisperses the coagulated fraction into a very opalescent solution which cannot be separated by centrifugalizing at ordinary speeds. This mixture yields a precipitate both with antinative-albumin and with antiheat-denatured-albumin rabbit sera.

[1] J. Amer. Chem. Soc., 1933, **55**, 3051.

Immunization was carried out in rabbits by the subcutaneous route. The animals were tested for degree of immunization both by intradermal injection and by precipitation with the serum obtained after bleeding. Excellent agreement both with respect to degree of immunization and to antigenic specificity was observed in the results of the Arthus phenomenon, in the intradermal testing, and in serum precipitation.

Further Report on a Cancerous Disease of the Kidney of Frogs.—Balduin Lucké (Laboratory of Pathology, University of Pennsylvania). In about 2 per cent of leopard frogs (Rana pipiens) there has been observed a neoplastic disease which manifests itself by the occurrence of unencapsulated whitish tumors in the kidneys. In the majority of the cases these tumors have the histologic appearance of adenocarcinoma.

Two hundred and four frogs with such tumors have been studied. The disease occurs in both sexes and in either of the kidneys with approximately the same frequency. The tumors are commonly multiple and in about one-half of the series they occur bilaterally. They vary in size from minute nodules to masses several times larger than normal kidneys. While the new growths are locally destructive and infiltrative they very rarely metastasize.

In the majority of the tumors there are present characteristic nuclear changes, namely condensation of chromatin at the nuclear periphery and very numerous and prominent acidophilic inclusion bodies lying within nuclei which otherwise appear almost empty. The inclusions are of the same general appearance as those of herpes, chicken-pox and certain other virus diseases. They occur only in the epithelial cells of the tumors. Such inclusion bodies are currently regarded as presumptive evidence of the activity of a virus; however, actual proof of the existence of such virus and of its relation to the tumor cannot as yet be furnished.

Material from 24 different tumors has been transplanted by various methods and into several regions of a total of 478 frogs; while in a relatively small number of animals the transplants have survived for upward of 3 months and exhibited some evidence of growth, no massive tumors have developed at the site of inoculation. However, in a number of the animals large tumors did arise in the kidneys; this may or may not be evidence of transmission. It should be pointed out that if the causal agent of this neoplastic disease be a virus it would be expected to localize and produce, under experimental conditions, lesions in that tissue (in this case kidney) where the spontaneous growths occur. Further experiments are necessary to establish the true nature of the tumors. They appear to be promising material for various studies on new growths.

Some Characteristics of Intestinal Lactase.—F. A. Cajori (Laboratory of Physiological Chemistry, University of Pennsylvania). A lactose-splitting enzyme was invariably found in water extracts of the mucosa of the duodenum and jejunum of adult dogs. Juice from a Thiry loop of the colon did not contain the enzyme. Jejunal juice showed feeble lactase activity.

Intestinal lactase exhibited maximum activity in acid solution

between pH 5.4 and pH 6. Its activity was inhibited by glucose but not by galactose.

A determination of the Michaelis constant indicated $K_s = .0056$. According to the theoretical significance of this constant, intestinal lactase has a higher affinity for its substrate than intestinal invertase.

Lactase was found to be adsorbed readily from slightly acid solution by aluminum hydroxid or ferric hydroxid.

A lactase was also found in water extracts of the liver. The enzyme activity of such extracts was about one-fifth that of intestinal mucosa extracts.

The lactase activity of intestinal mucosa extracts and intestinal juice accounted for less than one-half of the lactose that disappeared from a jejunal loop during absorption trials with this sugar in the intact animal. The finding of a liver lactase may be significant in revealing a further mechanism for lactose hydrolysis.

Factors Influencing the Secretion of Tracheal Mucus.—JULIAN JOHNSON (Laboratory of Surgical Research, University of Pennsylvania). Reference was made to the work of Florey and Wells in which a new method for observing the secretion of tracheal mucus was described. By this method Florey, Carleton and Wells found that stimulation of the peripheral end of the recurrent laryngeal nerve, or of the central end of one cut vagus, will cause secretion of tracheal mucus. They also showed that pilocarpin will produce a secretion of mucus which can be prevented by atropin.

By varying the method of Florey and Wells, we have demonstrated that stimulation of the peripheral or central end of the superior laryngeal nerve will cause a secretion of mucus. It was also shown that when an irritating substance comes in contact with the tracheal mucosa, mucus is secreted, due both to direct irritation and reflex stimulation of the mucous glands.

Notice to Contributors.—Manuscripts intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively.

All manuscripts should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. Illustrations accompanying articles should be numbered and have captions bearing corresponding numbers. For identification they should also have the author's name written on the margin. The recommendations of the American Medical Association Style Book should be followed. It is important that references should be at the end of the articles and should be complete, that is, author's name, journal, year, volume (in Arabic numbers) and page.

Two hundred and fifty reprints are furnished gratis; additional reprints may be had in multiples of 250 at the expense of the author. They should be asked for when the galley proofs are returned.

Contributions in a foreign language, if found desirable for the JOURNAL, will be translated at its expense.